The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME I DECEMBER, 1941 NUMBER 12

Basal Heat Production in Hypogonadism in Men and Its Increase by Protracted Treatment with Testosterone Propionate

[Hypogonadism]

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IN SEVERAL STUDIES during the past two years we have recorded slight but consistent increases in the basal metabolic rates of eunuchoids treated with testosterone propionate (1, 2, 3). This effect has paralleled other and often more striking metabolic events such as gain in weight, reduction in urinary excretion of sodium, chloride, potassium, inorganic phosphorus, water, total nitrogen and creatine (2, 3) and increased urinary excretion of androgens and estrogens (4). In 5 brief experiments on 4 hospitalized patients, with treatment lasting from 9 to 14 days, heat production, expressed in total Calories per hour exceeded base line levels by 8 to 9% in all instances save one in which the excess was 14% (2, 3). A 5th patient (*H.S.*) who differed from the others in having a gross demonstrable pituitary lesion showed no such response to the androgen (2). The heat production of one eunuchoid (*N.T.*) treated in the outpatient department showed no change during the first 10 days of treatment but increased 19% by the 40th day (1), thus suggesting that more decisive data could be secured by protracted experiments. Thompson and Heckel's experience is in agreement with this as they chart a rise in basal metabolic rate of about 20 points occurring a little short of 2 months after starting treatment of an 18-year-old eunuchoid with 25 mg. of testosterone propionate daily. They also speak of increases up to 30 points with heavier doses but have recorded no details as yet (5). Recently McCullagh and Rossmiller (6) have observed striking increases of the basal metabolic rate of eunuchoids receiving up to 300 mg. of methyl testosterone orally daily, the values reaching as high as +40%. In the castrate dog however Kochakian and Murlin (7, 8, 9) found that urinary androgens, androstenedione, and testosterone and its acetate have no consistent calorigenic action despite the qualitative and quantitative similarity of the reaction of nitrogen metabolism to that in man.

In this paper we have assembled our previously unreported data on the energy metabolism of 7 hypogonad men treated for long periods with testosterone propionate[1] given usually in 25 mg. doses intramuscularly 3 times weekly. One of these patients (*P.N.*) was a castrate, the others eunuchoids.

Received for publication October 3, 1941.

[1] The testosterone propionate was generously provided by Dr. Erwin Schwenk and Dr. Max Gilbert of The Schering Corporation, Bloomfield, N. J.

In none did physical or laboratory examination, including roentgenograms of the sella turcica and visual fields, provide conclusive evidence of a gross pituitary lesion. In one (*D.V.*) optic atrophy had been present since birth and some associated pituitary defect may have occurred but proof is lacking. In another (*J.K.*) a history of an inflammatory lesion of the testes during adolescence was obtained, but the studies of our associates Messrs. John Evans and Roger Varney in the Department of Biochemistry provided no evidence of such increased urinary excretion of gonadotropic material as one would expect from a primary testicular lesion. Indeed no gonadotropic activity was found in the alcohol precipitate of his urine, assayed by the response of uterine weight of the immature mouse. Thus the etiology of the eunuchoidism in all instances remains obscure.

During the course of the metabolic studies these people responded to the injected androgens by growth of the external genitalia and the prostate gland, increased frequency of erections, growth of body hair and deepened voice just as have others in our experience (1) and in that of many others. We have furthermore considered the basal metabolic rates of our entire series of untreated hypogonad men in some detail to attempt such comparison between the calorigenic properties of the testis itself and injected androgens as is possible with our material.

METHODS

Basal metabolism determinations were made either by the open circuit method (10) or by the closed circuit employing the Benedict-Roth apparatus. With the second method the routine procedure was to obtain two satisfactory tests, each 7 minutes in duration, the mouthpiece and noseclip (or mask) being removed after each test to allow the patient a short rest. The line representing the oxygen consumption was drawn independently by 2 people with all the precautions pointed out by Roth and Buckingham (11). If the 2 tests agreed within 5% they were averaged to arrive at the B.M.R., otherwise a third test was done and the average of such tests as fell within the above limits of error used. This routine inevitably results in partial training of the patient, and the discarding of exceptional values. Thus unusually high first rates and more rarely unusually low first rates are discounted. Isolated lowest rates are never selected as such. The average of two or more tests minimizes the errors of reading and the insistence upon such close agreement serves not only as a test for tightness of the mouthpiece and noseclip but also as a method of checking the relative degree of relaxation of the patient and the accuracy with which the technician controls the individual.

Although the Benedict-Roth procedure is technically more simple than the gasometer and is accordingly the method of choice in this laboratory, it must be recognized that there is a small group of individuals who cannot be trained to give satisfactory respiratory graphs. Satisfactory graphs must have a slope of approximately the same magnitude from minute to minute; consequently, changes in volume of the functional reserve air will vitiate the accuracy of the line drawn to measure oxygen consumption. Such individuals with habitual respiratory irregularities were always studied by the gasometer method, where irregularities, unless extreme, are reflected more in the CO_2 output than in the oxygen consumption. In satisfactory subjects there is a close correspondence between values obtained by the 2 methods as shown by Carpenter (12). Sixty-five comparisons in 4 such patients gave an average rate for the gasometer 1% above that of the Benedict-Roth. In 12 determinations the values were the same, in 21 the gasometer averaged 3.5% higher, in 32, 2.6% lower. The Mayo Foundation standards as developed by Boothby, Berkson and Dunn (23) were used in calculating the B.M.R.

In all patients to receive treatment repeated B.M.R. tests were made until a stable base line was achieved. With the exception of *J.K.* all of the patients were engaged in their usual activities and were studied in the outpatient department. *J.K.* was studied while in the hospital. He was placed on a weighed diet containing the same food each day, designed according to our previous procedure (3). This diet allowed him 323 gm. of carbohydrate, 80 gm. of protein, 110 gm. of fat, 4 gm. of added NaCl per day, yielding in all 2,602 Calories, sufficient to maintain his weight between 76.7 and 77.3 kg. (168–170 lbs.) during the weeks prior to treatment. His nitrogen intake of 12.7 gm. when compared to the average urinary nitrogen excretion of 11.64 gm. provided for approximate nitrogen equilibrium when an allowance is made for fecal nitrogen. His fluid intake was constant and included 1,500 cc. of drinking water until July 6 (*day 48* of treatment) when the warm weather made it necessary to allow water ad libitum. During this period some sweating occurred, introducing a slight error into the approximate balance. The patient was up and about through the day engaging in fairly regular mild recreational activity.

His urine was collected in containers to which enough 5 N H_2SO_4 was added to insure acidity. Total nitrogen, creatinine and in a few instances creatine were done on aliquots by methods previously cited (3). Androgen assays by the capon's comb technique were performed on the remainder of the urine by Messrs. George Beach and Robert Coffman under the direction of Dr. F. C. Koch according to methods previously described (13). These values together with those for 17-ketosteroids have already been given by Holtorff and Koch (14).

DISCUSSION

The data of table 1 and figures 1 and 2 are in agreement with that previously reported (1, 2, 3, 5) in demonstrating an increase in basal heat production during treatment of the hypogonad man with testosterone propionate intramuscularly. With moderate dosage, 25 mg. three times weekly, for long periods this influence is suggested in all of the 7 experiments on 6 subjects included here but there is great variation in the intensity of response (table 1, fig. 1). The rise in basal heat production may be conspicuous as in *D.H.* (*exp.* 1) or in *L.T.*, in each of which the increase in total calories per hour amounted to 23% and the B.M.R. rose 16 or 17 points, or it may be negligible as in *D.H.* (*2nd exp.*) or *D.V.* in which the increase in total Calories was only 6 to 8% and the rise in B.M.R. only 4 to 5 points. Even when the eventual effect is substantial the first 2 weeks of treatment may show little change (*D.H. 1st exp.*, *H.K.*) and it is only subsequently that heat production increases. On the other hand the response may be prompt at first (*L.T.*) with only a gradual rise thereafter. Among those in which the effect is well defined (*D.H., 1st experiment*, *H.K.*, *L.T.*) the fastigium is reached between the 2nd and 5th month with little subsequent change. A similar limitation also commonly occurs in the weight gain as we have noted before (1) and is illustrated again by *D.H.*, 1st *experiment*, *D.V.* and *L.T.* (table 1).

Figure 2 obtained on *J.K.* while he was in the hospital on a constant diet and with regulated activity discloses a definite elevation in heat production (11% in total calories per hour, 8 points in the B.M.R.) toward the end of the 2-week treatment period with the minimal dose of 5 mg. daily, and a still more considerable effect (16% increase in total calories, 11 points in the B.M.R.) with 10 mg. per

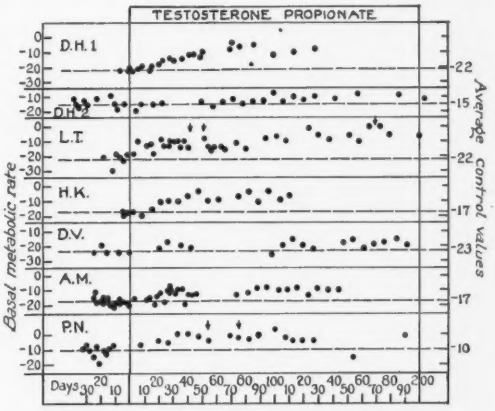

Fig. 1. Effect of protracted treatment with testosterone propionate on B.M.R. of hypogonad men. *P.N.* is a eunuch, the others eunuchoids. Testosterone propionate was given intramuscularly 3× weekly with the following exceptions. *L.T.* received no treatment between the first 2 arrows and 25 mg. 4× weekly after the 3rd arrow. *P.N.* received 50 mg. 3× weekly between the first 2 arrows and 25 mg. 2× weekly after the 2nd arrow.

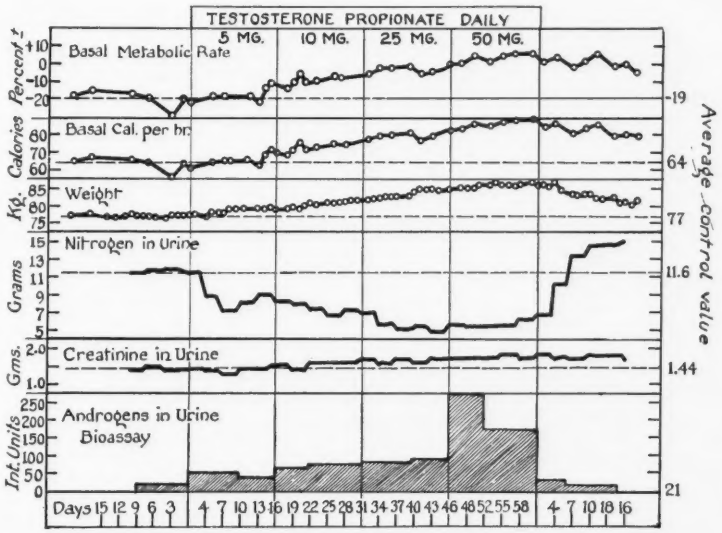

Fig. 2. Effects of varying dosages of testosterone propionate on basal heat production, body weight, urinary nitrogen, creatinine and androgens in the eunuchoid *J.K.* The data on androgens have been recorded previously by Holtorff and Koch (14).

day. The maximum influence of a 38% increase in total calories, 24 points in the B.M.R. was observed toward the end of the 2-month treatment period when the patient was receiving 50 mg. of testosterone propionate per day. The progressive augmentation of heat production through the course of the experiment should not be unreservedly ascribed to the graded increase in dosage because, as already noted, oxygen consumption may gradually increase during the first 2 months of treatment when dosage is constant (*D.H. experiment 1, H.K.*, table 1, fig. 1). Distinct changes in the respiratory quotient were not observed (table 1).

The details of the decline in heat production after the discontinuance of treatment have been insufficiently studied. In *L.T.* (table 1) 4 months after stopping treatment, the B.M.R. had declined only 11 points and was still 6 points above the original level. In *D.H.* the first perod of treatment with testosterone propionate by injection was followed by 3 months of testosterone by inunction during which time the subject's absence from town precluded measurement of his oxygen consumption. The 6-week control period following this and preceding the second injection experiment however showed no progressive decline in heat production. The average B.M.R. during this time was −15, 7 points above that of the initial control period and 9 points below the peak of the first treatment period (table 1). Only a slow and moderate decline in heat production after

TABLE 1. EFFECT OF TESTOSTERONE PROPIONATE ON HEAT PRODUCTION, RQ, PULSE RATE, BLOOD PRESSURE, BODY TEMPERATURE, AND BODY WEIGHT IN HYPOGONADISM

Averages for stated periods.

Period of treatment	No. of tests	Weight, kg.	Blood pressure mm. Hg	Pulse	Temp. °F.	R.Q.	Basal Heat Production Cal. per hr.	B.M.R %
P.N., eunuch, age 33 yr., height, 181 cm. (72 in.)								
Control	1st 2	76.8	110/70	80	98.2	0.91	81.5	+ 6
	10	76.5	109/71	75	97.9	0.77	68.5	−10
25 mg. test. prop. intramuscularly 3×weekly; 50 mg. 3×weekly, *days 54 to 75;* 25 mg. twice weekly, *days 75 to end*								
2 weeks	2	76.7	110/70	80	97.4	0.74	70.4	− 8
2 weeks	2	77.6	110/71	79	97.7	0.74	73.9	− 5
2 months	4	78.6	110/71	81	97.8	0.75	76.8	− 1
3 months	4	79.3	114/72	80	97.8	0.75	76.7	− 2
4 months	4	80.4	109/71	80	97.5	0.76	77.2	− 1
5 months	1	80.0	108/70	78	97.8	0.76	74.9	− 4
6 months	1	80.1	110/70	73	97.6	0.76	65.9	−16
7 months	1	81.3	110/70	80	97.4	0.79	77.7	− 1
D.H., eunuchoid, age 22 yr., height 177 cm. (70.8 in.)								
Control	6	63.2	95/63	55	98.2	0.74	56.5	−22
25 mg. testosterone propionate intramuscularly, 3×weekly								
2 weeks	6	64.0	98/60	57	97.9	0.76	57.0	−22
2 weeks	8	64.8	94/63	58	97.9	0.75	61.2	−16
2 months	12	66.1	100/62	61	98.2	0.77	63.5	−14
3 months	5	67.1	103/64	68	98.3	0.77	69.5	− 6
4 months	2	66.5	97/62	64	97.8	0.78	65.9	−11
5 months	1	65.4	102/66	64	98.4	0.78	67.3	− 8
D.H. 2nd experiment[1]								
Control	10	61.4	96/62	58	98.2	0.80	60.5	−15
25 mg. testosterone propionate intramuscularly 3×weekly								
2 weeks	2	60.9	97/60	60	98.0	0.83	58.6	−17
2 weeks	2	62.4	97/60	56	97.9	0.86	60.6	−15
2 months	2	63.5	101/66	61	98.1	0.79	61.9	−15
3 months	4	65.4	106/68	61	97.9	0.82	63.4	−13
4 months	4	66.1	108/70	59	98.0	0.79	65.3	−11
5 months	4	66.7	106/66	61	97.8	0.81	64.6	−12
6–11 months	6	67.6	102/64	58	98.0	0.80	66.1	−11
L.T., eunuchoid, age 32 yr., height 179 cm. (71 in.)								
Control	9	97.9	107/71	53	97.7	0.77	65.8	−22
25 mg. test. prop. intramuscularly 3×weekly; 25 mg. 4×weekly and reduction diet *day 172 to end.* No treatment *days 42 to 51.*								
2 weeks	6	98.1	103/71	58	98.0	0.75	72.0	−15
2 weeks	12	99.8	109/71	57	97.8	0.78	74.5	−13
2 months	19	99.5	107/67	55	98.0	0.76	74.0	−13
3 months	6	100.1	105/70	52	97.5	0.76	74.2	−13
4 months	5	101.0	106/63	51	97.5	0.78	77.7	− 9
5 months	8	100.4	99/66	56	97.9	0.76	80.6	− 6
6 months	6	99.4	101/62	59	97.9	0.80	80.7	− 5
7 months	6	94.4	102/60	45	97.2	0.75	76.8	− 7
8 months	2	91.7	90/59	46	96.9	0.79	73.4	−11

TABLE 1—*Continued*

Period of treatment	No. of tests	Weight, kg.	Blood pressure mm. Hg	Pulse	Temp. °F.	R.Q.	Basal Heat Production Cal. per hr.	B.M.R. %
L.T. post-treatment control[2]								
1 month	3	87.5	97/61	42	97.3	0.80	72.2	−10
2 months	2	85.6	93/63	47	97.7	0.83	70.6	−11
3 months	2	86.2	93/60	50	97.6	0.80	69.9	−12
4 months	2	86.2	92/61	51	97.3	0.80	66.5	−16
H.K., eunuchoid, age 26 yr., height 172 cm. (67.7 in.)								
Control	5	73.9	121/71	72	98.2	—	61.4	−17
25 mg. testosterone propionate intramusc. 3×weekly								
2 weeks	1	74.3	122/72	71	97.8		59.9	−19
2 weeks	3	75.5	119/72	72	97.9		65.7	−12
2 months	4	78.6	124/80	75	97.7		70.2	− 8
3 months	4	81.3	120/73	71	97.7		71.2	− 8
4 months	3	82.2	120/77	70	97.7		72.1	− 7
A.M., eunuchoid, age 23 yr., height 163 cm. (64 in.)								
Control	17	80.3	110/67	65	97.6		62.0	−17
25 mg. testosterone propionate intramusc. 3×weekly								
2 weeks	3	79.3	110/67	67	97.8		62.9	−15
2 weeks	6	79.7	113/68	68	97.5		64.6	−14
2 months	7	77.3	114/70	68	97.5		64.3	−13
3 months	3	73.2	114/71	68	97.7		63.7	−11
4 months	4	73.6	109/67	66	97.7		65.1	− 9
5 months	4	73.6	114/74	63	97.9		64.2	−11
6 months	4	75.2	113/71	67	97.5		61.8	−15
D.V., eunuchoid, age 34 yr., height 181 cm. (72 in.)								
Control	4	70.7	100/72	69	98.5	0.77	57.6	−23
25 mg. testosterone propionate intramusc. 3×weekly								
1 month	2	74.1	98/71	75	98.4	0.78	61.1	−20
2 months	2	74.6	96/65	74	98.1	0.77	60.2	−21
3 months	0	—	—	—	—	—	—	—
4 months	4	75.0	104/68	69	97.8	0.83	59.4	−21
5 months	2	75.4	103/71	66	97.8	0.85	59.6	−20
6 months	4	75.0	103/68	64	97.9	0.79	60.6	−19
7–13 months	8	74.2	100/66	67	97.7	0.78	60.8	−18
J.K., eunuchoid, age 26 yr., height 184 cm. (72 in.)								
Control	11	76.8	99/66	65	97.7	0.90	63.8	−19
Testosterone propionate intramusc. indicated dosage daily								
2 weeks (5 mg.)	7	78.4	102/69	67	97.7	0.85	65.5	−18
2 weeks (10 mg.)	8	80.2	103/68	73	97.8	0.88	71.7	−11
2 weeks (25 mg.)	6	83.1	102/65	79	97.8	0.80	78.4	− 4
2 weeks (50 mg.)	7	85.4	103/65	79	97.7	0.84	85.4	+ 3
No treatment								
2 weeks	7	83.5	100/66	70	97.4	0.94	82.6	+ 1
5 days	2	82.3	102/69	66	97.6	0.91	80.0	− 3

[1] Testosterone by inunction between end of experiment 1 and 6 weeks before beginning of treatment in experiment 2. No systematic alteration of heat production during control for experiment 2 which covers 5 weeks before start of treatment.

[2] 2 months treatment with testosterone inunctions intervened between end of injection period and post-treatment control period. No systematic change in heat production occurred during this time.

TABLE 1a. SUMMARY

Change in values during month of maximum effect on heat production

	Month	Weight	B.P.	Pulse		Tem °F.	R.Q.	Cal./hr.		B.M.R.
				abs.	%			abs.	%	
P.N.	4	+3.9	± 0	+ 5		−0.4	−0.01	+ 8.7	13	+ 9
D.H. (1)	3	+3.9	+08/01	+13	24	+0.1	+0.03	+13.0	23	+16
D.H. (2)	4	+4.7	+12/08	+ 1		−0.2	−0.01	+ 4.8	8	+ 4
L.T.	5	+2.6	−09/03	+ 3		+0.2	−0.02	+15.3	23	+17
H.K.	4	+8.1	+00/06	− 2		−0.5	—	+10.4	17	+10
A.M.	4	−6.7	−02/00	+ 1		−0.1	—	+ 3.1	5	+ 8
D.V.	7–13	+3.5	−00/06	− 3		−0.8	+0.01	+ 3.2	6	+ 5
J.K.	6–8 wks.[1]	+8.6	+02/00	+14	22	±0.0	−0.05	+21.6	34	+22

[1] Receiving 50 mg. per day at this time; while receiving 10 mg. per day total Calories increased 16%, B.M.R., 11 points.

cessation of treatment is suggested by this observation. *J.X.* who was described in detail in a previous publication (3) had an original B.M.R. of −30. On his return to the hospital in October 1939 three successive determinations showed values of −16 to −18. He had had vigorous treatment with testosterone propionate for 6 months and irregular treatment for 3 months preceding re-entrance and none for 2 weeks. Although the heat production during the height of androgen influence is unknown it is apparent that discontinuance of therapy for a brief time did not lead to a resumption of the original low values. *J.K.* (fig. 2) provides the most satisfactory account of the consequences of withdrawal. By 3 weeks after the last injection of testosterone propionate, the B.M.R. had declined about 6 points, as compared to the maximum rise of 24, and the total calories per hour had declined to 28% above the pretreatment base line as compared to a maximum rise of 38%. It is fair to say therefore that while a decline in heat production occurs after withdrawal of the androgen it is not rapid and that at least several weeks often elapse before resumption of the initial oxygen consumption. It is quite possible that the original level of heat production is never reached after the cessation of vigorous long continued treatment. Our data is not extensive enough to settle this point.

The mechanism of the rise in basal energy metabolism produced by testosterone propionate remains obscure. Basal body temperature is regularly unaffected even with the most considerable rise in heat production in our experience (38% increase in total Calories per hour, *J.K.*). While the basal pulse rate may increase in some individuals (*D.H., 1st experiment, J.K.*, table 1) in others no significant effect is apparent (*L.T., H.K.*, table 1). These irregularities in response occurred in the experience of McCullagh and Rossmiller (6) when large increases in heat production were induced with oral methyl testosterone. It is unlikely that increased secretion of thyroid hormone could be responsible for such increases in heat production without consistent modifications of the pulse rate. Furthermore Jones, McCullagh and Buckaloo (15) noted no decline in blood cholesterol which might be expected from thyroid influence. Both systolic and diastolic blood pressures are unaffected even after months of treatment.

Professor Murlin (personal communication) has suggested that augmentation of protoplasmic mass under the influence of testosterone propionate without increase in heat production per unit mass might account for the increase in caloric expenditure of the resting body. The gradual rise and fall in heat production fits well with such a view. We have already reviewed the evidence leading to our belief that such an increase in body tissues does occur (2, 3) and an important element in this evidence is illustrated by the reduction of urinary nitrogen excretion in *J.K.* (fig. 2). Neither the gain in body weight repeatedly induced by testosterone propionate, nor the increase in surface area estimations derived from this gain in weight can be taken to measure increase in protoplasmic mass, as certainly much of the weight gain is due to accumulation of extracellular water (2). More exact measurements of tissue mass are desirable. Even such data as we have concerning nitrogen retention and creatinine excretion give an indecisive, indistinct picture.

Following an estimate given by Shohl (16) that a healthy man contains 30 gm. of nitrogen per kg. of body weight, *J.K.* may have possessed 2310 gm. of nitrogen in his tissues before treatment. The 262.4 gm. estimated as retained during the 2 months of testosterone propionate therapy would accordingly yield an increase of 11.4% at a time when the basal heat production expressed as total Calories per hour had increased 38%. While such a calculation suggests that an increase in heat production per unit mass has occurred it falls far short of proving it. Our ignorance of the nitrogen content of the untreated eunuchoid body is absolute and the site of new protein deposited under the influence of the androgen is obscure. Should selective expansion of more actively metabolizing tissues occur then the increased protoplasmic mass would be of considerably greater significance in accounting for augmented heat production than the foregoing calculation would indicate.

Total urinary creatinine has been suggested as a measure of muscle mass and Palmer, Means and Gamble (17) and Talbot and associates (18) have established correlations between urinary creatinine and heat production in adults and children. In short experiments we have never felt that the creatinine excretion was significantly affected by testosterone propionate despite the clear-cut increase in body weight, decline in urinary nitrogen excretion and slight but distinct increase in heat production (2, 3). In the longer experiment on *J.K.*, however (fig. 2), urinary creatinine rose from an initial average level of 1.44 gm. per day to 1.77 gm. per day late in the second month. At the time of the maximum rise of 38%, in heat production expressed as total Calories per hour, creatinine excretion exceeded the base line by 19%, the ratio of estimated total basal Calories per 24 hours to mg. of creatinine rising from 1.06 to 1.23. The former approximates the usual ratio for adult men insofar as the limited information available permits a statement (17). After withdrawal of testosterone propionate, creatinine excretion was sustained at high levels for 2 weeks while heat production declined somewhat and the ratio given above declined to 1.12. Insofar as this single experiment goes, the suggestion of Dr. Ephraim Shorr (personal communi-

cation) that androgens should in time increase urinary creatinine has been borne out. Heat production however was in all probability increased somewhat more than would be expected from the increased creatinine excretion.

It seems likely in view of the foregoing that heat production may increase during treatment with testosterone propionate by virtue both of increased mass of actively metabolizing protoplasm and of increased heat production per unit mass. Much more decisive data is desirable however before any analysis of this difficult problem can be considered satisfactory. McCullagh and Rossmiller's (6) observation that 200 to 300 mg. of methyl testosterone daily, given orally, may raise the B.M.R. of the eunuchoid to as high as +40 in time is of great interest in this connection. It is rather difficult to believe that such an effect can be other than calorigenic in the strict sense at least in part. Data on the extent of nitrogen retention and the amount of creatinine excreted in the urine will be of importance in estimating the factor of expansion of actively metabolizing tissue during such striking increases in heat production. That nitrogen retention may be produced with methyl testosterone is apparent from the data of Jones, McCullagh and Buckaloo (15) as well as from an unpublished study of our own. The possibility that heightened muscular tone may play a rôle in the increase in basal heat production by androgens is not to be neglected, although there is no obvious evidence of its importance.

The failure of Kochakian and Murlin (8) and Kochakian (9) to demonstrate increase in the heat production of the castrate dog during treatment with androstenedione and testosterone and its acetate, despite the retention of amounts of nitrogen per kg. of body weight comparable to those in our eunuchoids may well lie in the brief duration of their treatment periods which usually did not exceed 3 days. While certain hypogonad men such as *L.T.*, may respond promptly to testosterone propionate, our more common experience even with continuous daily injections of 25 mg. of testosterone propionate was to observe only slight changes in B.M.R. during the first week of treatment (2). Figure 1 and table 1 show that as much as 3 weeks must often elapse before the increase in heat production becomes apparent when 25 mg. are given 3 times weekly. Thus the fat castrate dog of Kochakian and Murlin (7) in which repeated injections of urinary androgens produced an elevation of heat production in the neighborhood of 10% in experiments of 3 to 4 weeks' duration may be more typical of canine response in long experiments than their thin dog in which similar treatment was without effect. Further work on the dog is necessary to settle this matter.

The question must be raised as to whether amounts of testosterone propionate conceived as substituting for the normal testes have any influence upon heat production. Estimates of this figure are necessarily crude but two separate lines of evidence permit an approximation. Howard and Vest (19) estimate that 25 mg. of testosterone propionate, twice weekly, are required to repair and maintain the secondary sex characters of the adult hypogonad. The authors would be inclined to regard 75 mg. weekly, divided into 3 doses, as has been used in much of the work recorded here, as more often more nearly optimal, while McCullagh (personal communication) would place the amount somewhat higher still. Such differences in opinion are inevitable and relatively unimportant as decisive experience of an objective character is difficult to secure within this range of dosage. Fifty to 150 mg. of testosterone propionate weekly, when given in 25 mg. doses, intramuscularly, would cover most of the clinical estimates of the amounts substituting adequately for the normal adult testes.

Measurement of urinary androgens after the administration of testosterone propionate provides confirmatory data. Recent measurements of the urinary androgen excretion by the capon's comb technique[2] in 10 normal young men gave an average of 68 I.U. per day, range 29 to 108. The values correspond to previous estimates from this laboratory (13). The eunuchoid *J.K.* (fig. 1) excreted 21 I.U. per day before treatment, much the same as in several castrates. This would indicate relatively little contribution by this subject's testes to urinary steroids. With 5, 10 and 25 mg. of testosterone propionate per day, urinary androgens rose to averages of 43, 66 and 75 I.U. per day respectively. All of these values fall within the normal range, that with 10 mg. corresponding most nearly to the average normal. In 2 of 3 eunuchoids without proved pituitary lesions previously studied, 25 mg. of testosterone propionate daily elevated urinary androgens to 100 to 120 I.U. per day, values close to upper normal levels (4). Fifty mg. daily in *J.K.* gave clearly excessive amounts of urinary androgens. Hamilton (20) gives 20 mg. of testosterone acetate 6 times per week as necessary to achieve normal urinary androgens in hypogonad men in the experience of Dorfman and himself. Although this discussion may seem to involve a naive disregard of the uncertainties surrounding interpretation of urinary androgens, it is of interest that an estimate of the amount of testosterone propionate required to produce average normal amounts of urinary androgens, greater than 5 mg. per day and less than 25, does not depart widely from estimates based on production and maintenance of normal secondary sex characters. Furthermore, the fact that 25 mg. of

[2] Tests made in Dept. of Biochemistry by Beach, Coffman and Koch; unpublished.

testosterone propionate daily induced the maximum depression in urinary nitrogen possible in *J.K.*, while an influence on the nitrogen excretion of normal men can be readily obtained with added androgens (3) suggests that 25 mg. per day is more than the equivalent of the normal testis.

The 75 mg. of testosterone propionate weekly, divided into three 25 mg. doses, or the 10 mg. daily, which we have shown to increase heat production in this study, accordingly do not appear to grossly exceed levels of dosage replacing the activity of the normal testis.

TABLE 2. BASAL HEAT PRODUCTION OF MEN WITH HYPOGONADISM

Subject	Age, yr.	Height, cm.	Weight, kg.	First determination this series: Total Cal/hr.	First determination this series: Cal./sq.m./hr.	First determination this series: B.M.R.
			Eunuch			
P.N.	33	181	76.7	81.9*	41.8	+6
			Eunuchoid			
W.M.	21	180	79.3	68.2	34.4	−16
D.H.	22	177	63.5	56.0	31.5	−22
A.M.	23	163	80.7	64.0	34.6	−15
H.K.	26	172	74.8	61.9	33.3	−17
J.K.	26	184	76.2	62.1	31.5	−21
F.R.	26	179	73.7	65.0*	34.0	−15
J.X.	27	180	63.0	51.6	28.8	−28
N.T.	30	162	53.7	49.3	31.8	−19
N.D.	31	175	54.3	53.0	32.1	−18
L.T.	32	179	97.3	67.2	31.3	−20
D.V.	34	181	70.2	56.9*	30.1	−23
J.H.	36	182	78.8	61.8	31.2	−19
M.D.	52	159	51.2	55.5	36.7	0
Average of 13 eunuchoids						−17.9
Average of 32 normal, untrained men, age 20–39 yr., in this laboratory						−12.3

B.M.R. values are based on the Mayo Foundation Standards (20).
The Benedict-Roth apparatus was used except where* indicates the gasometer method.
In some cases determinations had been made months to years earlier than this study.

The extent to which the normal testis influences basal heat production may be studied by examining untreated adults with testicular insufficiency. Castrates are rare and no series available is sufficiently extensive to more than indicate that the B.M.R. is not unmistakably depressed. Thus *P.N.* of our group, age 33, had an initial B.M.R. of +6 and of −7 after training (table 2). McCullagh and Renshaw (21) provide the best series, 9 eunuchs with a range of +5 to −21, averaging −13. McCullagh and Lilga (22) in 5 eunuchs, presumably supplementary to the earlier series, give B.M.R. values of −17 to −22%, −15, −17, ±0 to −12%, and −23%, averaging −16%. These determinations were performed by a closed circuit apparatus, using the Aub-Dubois standard for calculation (McCullagh, personal communication). The somewhat low average may be subject to the same correction that applies to our own figures, a point to be subsequently considered.

More information is available about the eunuchoid, although the possibility is always troublesome that some obscure and undetected pituitary defect operating to depress the B.M.R. may accompany testicular insufficiency. The best we can say about our series in this regard is that careful clinical study detected no gross pituitary disease. The clinical features were solely those of hypogonadism. The initial B.M.R. of 13 such subjects ranged from 0 to −28, average −17.2, by the Mayo Foundation standards as given by Boothby and his coworkers (20) (table 2). Training of 11 of these subjects to give consistent readings yields an average B.M.R. of −21 (range −14 to −33) as compared to the average for initial tests of −16.2 (range 0 to −28) for these subjects. When an average of all satisfactory determinations on each subject is obtained the mean for 13 eunuchoids is −21 (range −11 to −30) by the Mayo Foundation standards.

Unfortunately for the sake of simplicity these low B.M.R. values of our eunuchoids cannot be taken at face value. For some time one of us (I.S.) has been acquiring data on the basal heat production of healthy men and women, students and members of the technical and professional staff of the University. The series is not large enough to comprise a formal standard but offers a useful comparison with our eunuchoids. Thirty-two untrained men between 20 and 39 years of age averaged 12% below the Mayo Foundation standard, the Benedict-Roth machine being used in the determinations. Twenty-eight women of corresponding type average 10% below the Mayo Foundation standard. Such gasometric determinations as are available on healthy men and women, together with our data on patients without disease presumed to affect metabolism, exhibit the same tendency. All determinations of this type were done by one of us (I.S.) by the same technique as is used at the Mayo Clinic.

This is not a unique experience. Stark's data on male students between 16 and 20 years of age, obtained with the Benedict-Roth apparatus, fall 10.3% below the Mayo Foundation standard (calculated by Boothby, Berkson and Dunn (23). Shock and Soley (24) in a preliminary report record gasometric determinations, averaging 3 determinations on each of 2 successive days. Their values for normal men fall 9.2% below the Mayo Foundation standard, for normal women 8.7% below. It should be recalled that the Mayo standards are based upon initial satisfactory tests. Partial training inherent in the proper use of the Benedict-Roth procedure, and in such a study as Shock and Soley's, would be expected to lead to somewhat lower values.

The fact remains that an addition of some 12 points more or less must be made to correct the initial B.M.R. of our eunuchoids for the low values of

normal men in our laboratory. Thus the average for 13 eunuchoids becomes −5.6, the range +12 to −16%, hardly a significant departure from normal, and suggesting little more than a tendency which only an extensive series could substantiate. McCullagh and Lilga's series of 13 eunuchoids (19, from tables 5 and 6) give an average of −11%, range of +1 to −21%, according to our interpretation of their data. The same type of correction for normals that we have applied may be applicable here.

The average influence of such amounts of testosterone propionate as are conceived as substituting adequately for the normal testis, —25 mg. three times weekly as in most of our subjects, or 10 mg. daily as in *J.K.*,—is to elevate the B.M.R. 10 points (range 4 to 17, table 1a, fig. 1, 2). Such an effect can only be detected by systematic serial study. Should the normal testis exert an effect of this intensity, isolated determinations on hypogonad individuals would not suffice to detect the departure from the standard, normal variations being what they are. A large series, greater than any now available is necessary. As it now stands we can only state that the B.M.R. values of our eunuchoids are not far from what one would expect if the normal testis exerts approximately the influence on heat production given by moderate dosages of testosterone propionate.

The changes in heat production during normal puberty cannot be said as yet to be precisely defined, both transient increases in B.M.R. and transient plateaus in the curve of the B.M.R. previously declining with age having been described (for review, DuBois, 25). The magnitude of the effects of physiological dosage of testosterone propionate in our experience corresponds fairly well to estimates of the influence of puberty on heat production thus far available. It is unlikely on the other hand that androgens have much to do with the greater heat production of the male relative to the female as this difference is established long before puberty.

SUMMARY

One eunuch and 5 eunuchoids in 7 experiments showed a maximum increase of 5 to 23% in basal total Calories per hour during protracted treatment with testosterone propionate, usually given in 25 mg. doses, intramuscularly 3 times weekly. The B.M.R. increased from 5 to 17 points.

One eunuchoid, in the hospital, received successively 5, 10, 25 and 50 mg. of testosterone propionate daily, each dose level for 2 weeks. An increase in total Calories per hour of 16% (11 points in B.M.R.) occurred at the end of the 1st month and an increase of 38% (24 points in B.M.R.) at the end of the 2nd month. From the nitrogen retention and increase in urinary creatinine it was judged that both increase in protoplasmic mass and increase in heat production per unit mass were probably operative in accounting for the augmented basal metabolism.

Initial B.M.R. of 13 eunuchoids averaged −17.9% (Mayo Foundation standards) and −5.6% by a correction of these standards for values obtained in normal men in our laboratory. It is pointed out that only a very extensive series could make such a deviation significant. On the other hand the average influence of doses of testosterone conceived as replacing the normal testis is to increase the B.M.R. 10 points. Only an extensive series of hypogonad man would permit detection of such an influence exerted by the normal testis.

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Rapid Growth in Height Produced by Chorionic Gonadotropin in a Dwarfed Infantile Identical Twin

[Gonadotropins and Growth]

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THERE IS NO DOUBT that animal experimentation plays a great part in the development of new thought in research medicine. One is, however, well acquainted with the shortcomings of observations so attained, when one attempts to duplicate the results in the clinic patient. It is therefore of advantage, whenever possible to illustrate certain phenomena through the use of the human subject.

It has been possible to corroborate in a human control subject some observations previously made in the study of the effects of sex and growth in a group of boys to whom chorionic gonadotropin had been given (1). The observations reported herewith are particularly significant because the subjects were a set of identical twins who presented similar developmental defects in sex and growth and the observation period extended over a prolonged period of time.

CASE REPORT

The twins, *Richard* and *Joseph P.* of Italian parentage, were first seen at the Children's Endocrine Clinic at Bellevue Hospital in March, 1935 at the age of 7½ years. The complaint by their father was that these boys were not growing sufficiently. Their delivery had been normal and there was nothing significant in their infantile history. They had had the usual childhood diseases. On examination they were fairly well nourished but not obese, not acutely or chronically ill, but showed definite stunting for their age. They were fairly active although their intelligence rating on the Stanford-Binet standard was 84 to 85%, classifying them as having a dull normal intelligence. Language difficulty was thought to be a factor in the above evaluation. The skin and hair were not dry. In both patients, the testes were resident in the scrotum but were hypoplastic; the external genitalia were infantile. Studies of osseous development at this time showed a retardation of two to three years, as compared with their chronological age (fig. 4A and B). However, the osseous development varied in the two boys. *Richard* was about one year behind that of his brother, *Joseph*. *Richard* was also about one-half inch shorter than his brother.

On May 8, 1940, Dr. Alexander S. Wiener of the Pathology Department of Bellevue Hospital established the identity of the twins on the following basis: "*Richard* and *Joseph* belong to Group O, type MN. They each resemble their father in appearance. The father belongs to Group O, type MN; the mother belongs to Group B, type MN. The twins have similar builds; both were at the time about 51 inches in height and weighed about 64 pounds. There was a strong facial resemblance between the twins so that they were difficult to tell apart. Both had the same shade of dark brown straight hair, and had brown eyes. The shapes of the nose, chin and ears were the same in both boys. Both had similarly shaped hands, and both bit their finger nails. There was a strong resemblance between the palm prints and finger prints. Finally, titration of the isoagglutinins Anti-A and Anti-B in the sera of the two twins showed these to be approximately equal titers."

In view of retarded ossifications, *Richard*, the slightly shorter boy was given thyroid. He received a standard brand of desiccated thyroid, ¼ to ½ twice a day for about 4 months between June 1936, and June 1937. During the time between October 1937

Received for publication June 6, 1941.

Read at the twenty-fifth annual meeting of the Association for the Study of Internal Secretion on May 3, 1941, Atlantic City, N. J.

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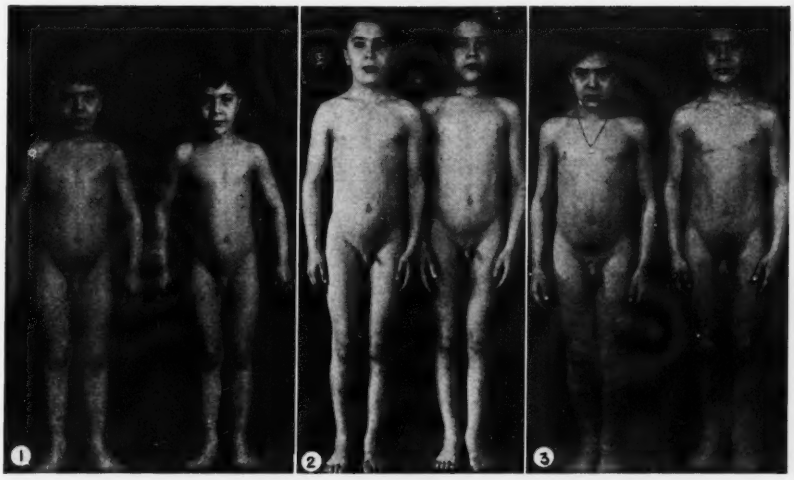


Fig. 1. IDENTICAL TWINS *J. P.* (left) AND *R. P.* (right) AT 7½ YEARS OF AGE; 3/21/35 BEFORE INSTITUTION OF THERAPY. Height 43 inches. Weight 43 pounds. Fig. 2. *J. P.* (left), *R. P.* (right) 10/38 11 years. Note persistence of genital underdevelopment. *R. P.* had received desiccated thyroid for about 2½ years. Fig. 3. *J. P.* (left), *R. P.* (right). 12/5/40. 13 years, 3 months. Height: *J.* 51 ¾", *R.* 53 ¾" *J. P.* served as control. *R. P.* received chorionic gonadotropin for 12 months. *R. P.* grew 4 inches in height, and puberal changes appeared. *J. P.* grew 1¼ inches and had no puberal change.

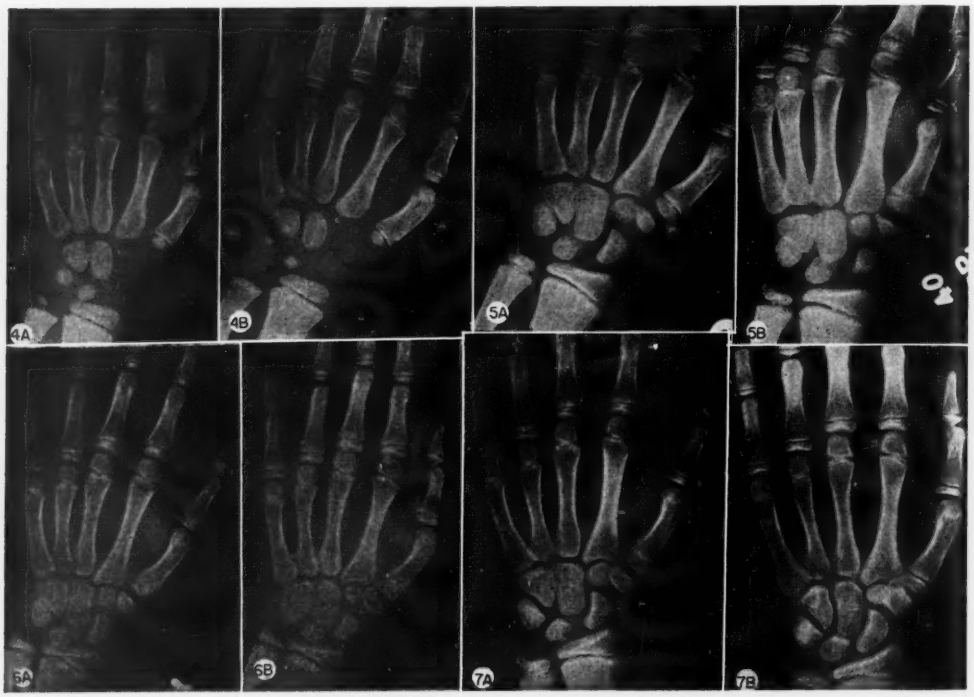
TABLE 1. EFFECT OF GONADAL STIMULATION ON GROWTH IN ONE OF IDENTICAL TWINS

Date	Age yr.:mo.	Height, in.	Wt.	Bone Age			Treatment
				Flory (6)	Todd (7)	Shelton (8)[1]	
			lbs.				
3/35	7:6	J—43	44	5:6–5:9	5:9	5:6–5:9	None
		R—42¼	42	4:0–4:6	4:3–4:9	4:0–4:6	None
6/36	8:9	J—45½	—	6:6	6:0	6:0	None
		R—44½	43½	5:6–5:9	5:9	5:6	Desiccated thyroid for few weeks
10/37	10:1	J—47¾	53¼				None
		R—46½	50				Desiccated thyroid for 3 months
6/38	10:9	J—48¼	54				None
		R—47½	50				Desiccated thyroid for the past yr. and for 1 yr. thereafter
12/39	12:3	J—50½	61				None
		R—49¾	59				Started chorionic gonadotropin
2/40	12:5	J—50¾	64	9:0	8:9–9:0	7:6	None
		R—50	60	8:9–9:0	8:6	7:0–7:6	On gonadotropin
9/40	13	J—51½	64	10:0	10:6	9:0	None
		R—52¾	62½	11:0	10:6–11:0	10:0–10:6	On gonadotropin
12/40	13:3	J—51¾	—				None
		R—53¾	—				Discontinued gonadotropin
1/41	13:4	J—51¾	67				None
		R—54¼	73				None
4/41	13:7	J—52¼	70	11:0	11:3	9:6–10:0	None
		R—54¾	79½	12:6–13.0	12:9	11:6	None

J—Control, untreated.
R—Treated.
[1] The author's assessment of Shelton's standards.

to October 1939 desiccated thyroid, ½ grain, was taken once a day for 6 months and twice a day for the remainder of the time.

Joseph was given no medication and was regarded as the control. At the end of that time, in spite of medication *Richard* had not increased in height any more than *Joseph* who was receiving no thyroid medication. It was felt that the thyroid medication was not efficacious so it was discontinued for the until a total of about 42,850 R.U. of chorionic gonadotropin had been given. No medication was given to *Joseph* who was again regarded as a control. In one year of treatment *Richard's* hypoplastic genitalia were stimulated with gonadotropin so that puberal changes were produced (fig. 3). In addition, his height had increased 4 inches. In the case of *Joseph* who received no therapy, the genital apparatus at the end of this same period was still infantile; he had grown



Figs. 4–7. ROENTGENOGRAMS SHOWING BONE AGE OF IDENTICAL TWINS. J.P. (left, A) R.P. (right, B). Fig. 4. Bone status of twins at 7½ years of age 3/35. A. J.P., estimated bone age 5½–5¾ years. B. R.P., estimated bone age of 4 to 4½. Fig 5. Age, 12 years, 5 months. 2/40. A. J.P., estimated bone age 7½–9. No treatment. B. R.P., estimated bone age 7–9. 2 months of treatment with chorionic gonadotropin. Fig. 6. Age 13 years 9/40. A. J.P. estimated bone age 9–10½. No treatment. B. R. P., estimated bone age 10–11. 9 months of treatment with chorionic gonadotropin. Fig. 7. Age 13 years, 7 months. 4/41. A. J.P., estimated bone age 9½–11. No treatment. B. R.P., estimated bone age 11½–13, 4 months after termination of active therapy.

next 2½ years. During the entire period of 4½ years each boy grew about 7 inches, *Joseph* still exceeding *Richard* in height, by about ¾ of an inch. During this same period there was very little change in their genital development. At this time, in December, 1940, when the boys were 12 years and 5 months of age, chorionic gonadotropin[2] was given to *Richard* who was still the shorter boy. Two hundred to 500 R.U. were given fairly regularly, three times per week in height 1¼ inches. *Richard* who originally was shorter by ¾ of an inch now exceeded his brother who had grown 1¼ inches spontaneously, by 2 inches. During this 1-year period of treatment, *Richard* had gained 14 pounds in weight, whereas *Joseph* who was untreated gained only 6 lbs. In addition, in September 1940 after 9 months of treatment with chorionic gonadotropin the osseous development in *Richard* had advanced so that the bone lag was 2 instead of three years. The untreated boy, *Joseph*, at this time showed a 3-year instead of the 2-year lag existing in 1935 at the chronologic age of 7½ years.

[2]Pregnyl, a chorionic gonadotropin in a powdered state, was kindly supplied through the courtesy of Doctors B. L. Josephy and Leo Pirk of Roche-Organon Inc.

In April 1941, *Richard* had not attained a bone status equivalent to his chronological age. Thereafter therapy was discontinued for *Richard* and the progress of both observed. At the time of this writing, about 4 months after termination of active therapy (April 1941) *Richard* had grown another inch in height, whereas *Joseph* had gained only half an inch.

DISCUSSION AND COMMENT

In view of the physical and osseous retardation in these patients, the diagnosis of subclinical or masked hypothyroidism had to be considered (4). This was ruled out quite definitely by the lack of any striking response to the therapeutic test with desiccated thyroid administered to *Richard*.

The diagnosis of hypopituitarism also was considered in view of the stunted growth and sexual infantilism. One should be wary of such a diagnosis in young children since the criteria of stunted growth and sexual infantilism though presumptive, are not conclusive evidences of hypopituitarism. Furthermore, even if one were to assume that this was hypopituitarism there is not available a potent commercial anterior pituitary extract to stimulate growth.

In view of past experiences in a group of cases with the use of chorionic gonadotropin for stimulating sex and growth as reported in two recent communications (2, 3), this case was treated with chorionic gonadotropin with the knowledge that stimulation of the gonads might act as an intermediary for inducing growth. The result obtained in this case with the patient *Joseph* as a control, corroborates the previous findings. It indicates that growth in height may be indirectly accelerated when sexual development is evoked through gonadal stimulation.

In *Richard*, while sexual development was taking place, and puberal changes were being evoked there was a concomitant acceleration in linear growth, the height spurt being over three times that of the untreated identical twin. This was for him normally a growth equivalent of more than three years. Whether this increase will continue, or will exceed the newly attained height curve cannot be stated, although experience with similar cases permits the prediction that there is a good chance that regression will not occur soon and that acceleration may be maintained for some time after therapy has been discontinued.

Past experience also permits the assumption that

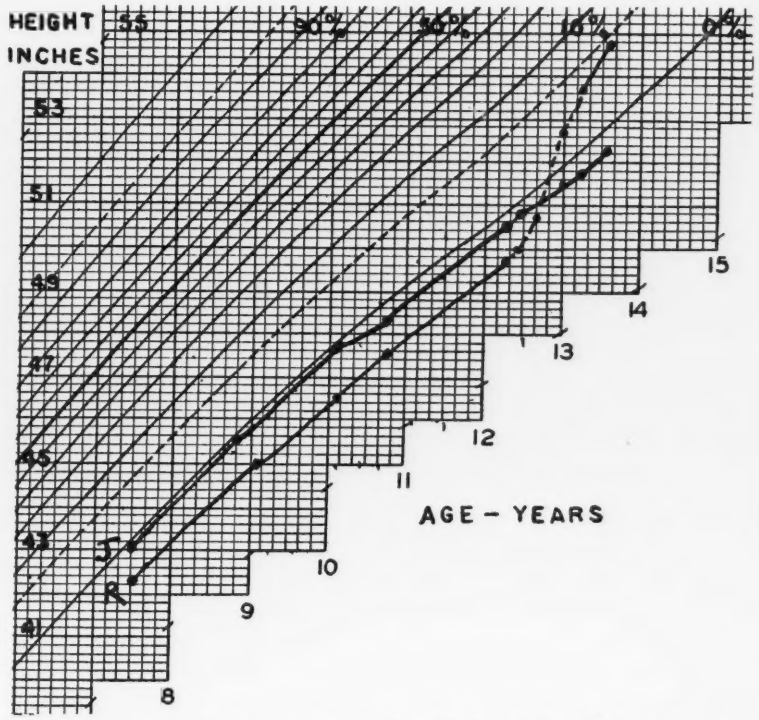


Fig. 8. GROWTH CURVES FOR IDENTICAL TWINS *J. P.* AND *R. P.* ON BURGESS' CHART. *J. P.* was not treated and served as control for his brother *R. P.* who was subsequently treated with chorionic gonadotropin. Broken line indicates period of gonadotropic therapy.

the growth will not soon be terminated in this boy. This is based on the fact that in previous cases, even though precocious puberal changes were produced, there was no alarming evidence of premature closure of epiphyses. In the case of these twins, *Richard* who had been treated intensively, is continuing to grow with no evidence of epiphyseal closure although puberal changes have taken place.

It should be pointed out that *Richard* has not only overcome the osseous lag which existed between him and his untreated brother but he has now exceeded the bone status attained by his untreated brother, although in the case of *Richard* it is not as yet up to his chronological age.

The above results indicate that the termination of linear growth normally seen with complete sexual maturation need not occur as the result of intensive stimulation with gonadotropic therapy which produced some puberal changes.

One also should not confuse the progress made in linear growth and osseous development in this case with the pathologic picture of macrogenitosomia praecox already discussed in a previous report, wherein it was indicated that in such cases there is uncontrolled gonadal stimulation with premature closure of the epiphyses (2).

In this case one need not therefore worry too much about the relative advance in ossification for even if this boy should maintain this accelerated curve and gain 4 inches in the next year I feel, even at the risk of advancing his osseous status somewhat, that there will be no dire result.

It is also worthy of note that the treated patient gained 14 pounds in one year whereas the untreated brother gained only 6 pounds. An increased increment in weight during treatment with gonadotropin alone has been observed previously (1).

It is significant in spite of contrary opinion, that chorionic gonadotropin is effectual not only in cases of cryptorchidism but is also effectual in instances of hypoplastic gonads and genitalia.

It is unlikely that the sexual development which took place in *Richard's* case was coincidental and would have occurred spontaneously in that period of time.

SUMMARY

A set of identical twins was studied for 6 years because of existing similar endocrine stigmata dwarfism and sexual infantilism. Although these boys grew in height, their growth was not commensurate with the average normal increment in height for their age. It was decided to treat one of these twins and to regard the other as a control. One of these boys, the shorter one therefore, was placed on desiccated thyroid for about a two-year period because of his more retarded ossification and other developmental deficiences. When no apparent difference in skeletal or sexual development was noted as a result of thyroid therapy the diagnosis of primary hypothyroidism was discarded.

Hypopituitarism was considered but there were no potent pituitary products for the purpose available. Chorionic gonadotropin was administered in order to stimulate growth through stimulation of the gonads. In one year of therapy, the treated boy showed marked gonadal and genital growth and puberal changes. There was a linear growth spurt of 4 inches. This was a height increase of more than 3 years accomplished in 1 year based on previous performance. The identical twin, who served as the untreated control, grew only 1¼ inches spontaneously during the same period. The treated twin gained 14 pounds in weight in one year while the untreated one gained only 6 pounds during the same period. The osseous development which was retarded in both boys, was advanced by treatment so that the lag in the treated brother was diminished and his bone status though not up to his chronological age, now exceeded that of his untreated brother.

The writer acknowledges the splendid cooperation of Misses Sensenbach and Soscia, and Mrs. Marie L. Parker of the Nursing Staff of the Children's Clinic.

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Effect of Pregnancy-Urine Hormone and Vitamin B-6 on the Blood and Bone-Marrow Pictures in Primary Erythroblastic Anemia (Cooley)

[Gonadotropins and Anemia]

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SINCE OUR ORIGINAL paper concerning the hypothetical basis for the effect of various hormonal substances (1) on body tisues, several observations on the effect of pregnancy-urine gonadotropin (prolan B) on certain mesenchymal structures have been made (2). It was felt that a study of the bone-marrow picture and its resulting peripheral blood changes following the use of these hormones would afford additional information. To this end several cases of primary erythroblastic anemia have been selected for observation.

The work of Papanicolaou and Falk (3) demonstrates the stimulating effect of androgen and pregnancy-urine gonadotropin on the general musculature in guinea pigs. Antopol and Schotland (4) have described the beneficial influence of vitamin B-6 therapy on humans suffering from chronic muscular dystrophy. It was decided to study the parallel effects of vitamin B-6 and prolan B on the hematopoietic system in primary erythroblastic anemias.

There is still confusion regarding the pathological basis of Cooley's anemia. Some evidence points to the presence of a hemolytic process with compensatory marrow hyperplasia (5). The existence of an abnormal hyperplastic marrow process resulting in the appearance of immature cells in the peripheral blood has been suggested. Whipple and Bradford (6), among this latter group, express the belief that the bone marrow process may be the result of vitamin or endocrine disturbance.

In the event that there is a hemolytic process stimulation of the bone marrow should lead to greater compensation by marrow hyperplasia which would combat the existing anemia.

Received for publication September 30, 1942.

CASE REPORTS

Case 1. H. B., a female child of Greek parentage, was born June 1937, one of identical twins. The twin died at 1 month of age with a diagnosis of lobar pneumonia.

H. B. was hospitalized at 20 months of age for pneumonia at which time hepato-splenomegaly and severe anemia were noted. She was readmitted at frequent intervals for upper respiratory infections and during these periods received various forms of therapy, including 3

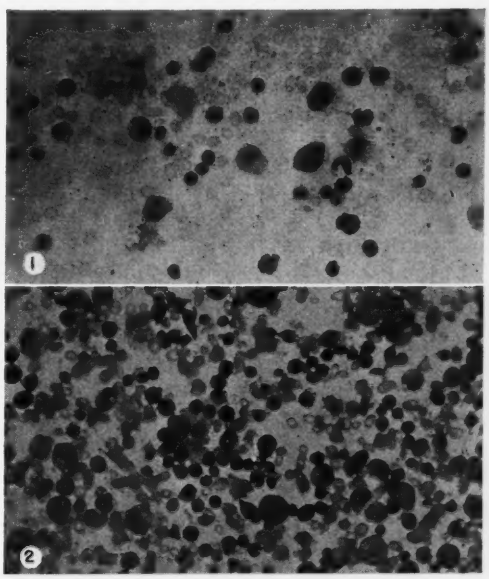


Fig. 1. MARROW SMEAR FROM *case 1*. May 4, 1941. Smear made before therapy. Fig. 2. MARROW SMEAR FROM SAME CASE FOLLOWING THERAPY WITH PREGNANCY-URINE PROLAN AND VITAMIN B-6 Jan. 13, 1941.

blood transfusions, thiamin chloride, iron, liver and vitamin D. It was not until December 1939 that she showed the typical bone changes of Cooley's anemia.

She was first seen by one of us on April 29th, 1940 at which time she showed the clinical picture of Cooley's anemia with characteristic bone changes on roentgenogram and the following blood picture, erythrocytes 2,350,000 per cu. mm.; Hb 5.8 gm. per 100 cc., and 8 normoblasts per 100 white blood cells.

She was placed on pregnancy-urine hormone therapy hormone or vitamin treatment whatsoever, but was given the only blood transfusion of the entire period of observation.

An analysis of the erythrocytic changes in figure 3 shows a definite rise in number of red blood cells following the use of pregnancy-urine hormone alone, a rise of lesser degree with combined therapy, a maintained level with vitamin B-6 alone, and a regression following the removal of all therapy.

Bone-marrow aspiration on May 4, 1940 revealed a

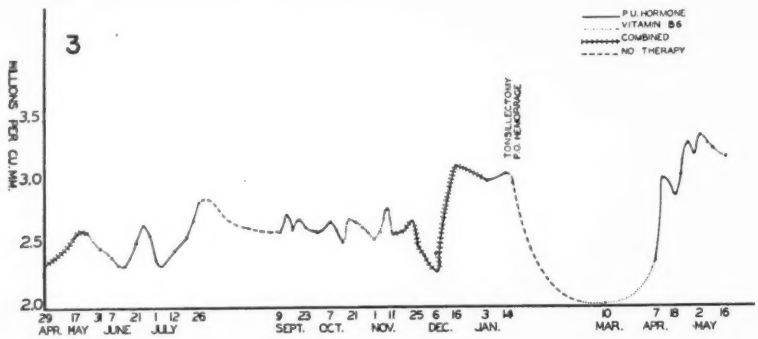
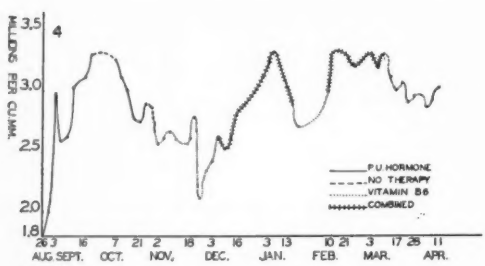

3
P.U. HORMONE
VITAMIN B6
COMBINED
NO THERAPY
MILLIONS PER CU. MM.
3.5
3.0
2.5
2.0
TONSILLECTOMY P.O. HEMORRAGE
29 17 3 7 21 1 12 26 9 23 7 21 1 11 25 6 16 3 14 10 7 18 2 16
APR. MAY JUNE JULY SEPT. OCT. NOV. DEC. JAN. MAR. APR. MAY

Fig. 3. Graph of the erythrocyte changes in a child with Cooley's anemia (*case 1*). Therapy with pregnancy urine hormone and Vitamin B-6.

(about 600 R.U. per week) and vitamin B-6 (50 mg. daily) for about 4 weeks, alternating with periods of pregnancy-urine hormone alone and with periods of vitamin B-6 alone. In February 1941, she was hospitalized for tonsillectomy with post-operative hemorrhage and upper respiratory infection. During this period she received no characteristic normoblastic marrow (fig. 1). A second marrow study on Jan. 13, 1941, immediately following a course of combined therapy and pregnancy-urine hormone alone, showed a marked hyperplasia, especially evident in the number of immature erythrocytic elements (fig. 2).



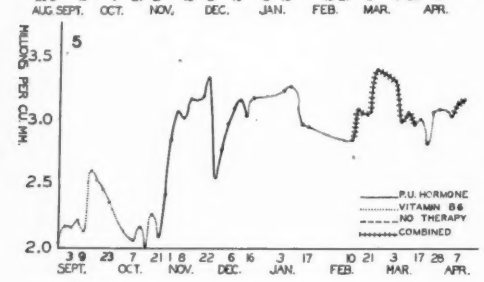


Fig. 4. Graph of erythrocyte changes in a child with Cooley's anemia (*case 2*). Fig. 5. Graph of erythrocyte changes in a child with Cooley's anemia (*case 3*).

Bone Marrow Findings

	May 4, 1940	Jan. 13, 1941
Total nucleated cells	236,000	690,000
Megakaryocytes	150	350
Segmented neutrophiles	16.5	13.5
Non-segmented neutrophiles	31.0	31.5
Lymphocytes	9.0	3.5
Monocytes	—	—
Eosinophiles	—	1.0
Basophiles	—	—
Neut. myelocytes	38.5	43.0
Eos. myelocytes	—	0.5
Myeloblasts	1.0	3.5
Plasma cells	1.5	0.5
Myelogones	2.5	3.0
Normoblasts (per	174.0	262.0
Erythroblasts 100	17.0	31.5
Megaloblasts W.B.C.)	2.0	13.0

Clinical observations included the cessation of enuresis in the first month of treatment, more rapid growth of cephalic hair, stronger voice, and greater general muscular development.

Case 2. N. P., a male child of Greek parentage, an identical twin with *case 3*, was born May 10, 1938. Birth weight was 5 pounds. He was bottle-fed and showed no apparent illness until 10 months of age, at which time a severe anemia was noted. He attended the Hematology Clinic at the New York Hospital where the diagnosis of

Cooley's anemia was made. He received the various forms of recognized treatment with little change.

He was first seen by one of us Aug. 19, 1940, at which time he presented the following picture. Mongolian facies, marked pallor, weakness in walking, left cryptorchidism, enuresis, but no palpable spleen or liver. Roentgenogram showed characteristic bone changes and the blood picture showed erythrocytes 1,875,000 per cu. mm. Hb. 5.2 gm. per 100 cc., and 13 normoblasts per 100 white blood cells.

Treatment in the form of pregnancy-urine hormone alone (about 600 R.U. per week) was begun. Combined treatment was then alternated with periods of vitamin B-6 alone (fig. 4). No blood transfusions were given during the entire period of observation.

Analysis of the erythrocytic changes shows the most marked rise during the period of pregnancy-urine hormone therapy alone. There was a tendency to regression when this was continued beyond 3 or 4 weeks. There was a fair rise during the period of combined treatment and a maintained level with vitamin B-6 alone.

A bone-marrow study on Nov. 3, 1939, at the New York Hospital, revealed a fairly typical normoblastic marrow. Sternal aspiration performed on Oct. 21, 1940, after the initial period of pregnancy-urine hormone therapy revealed a marked hyperplasia of erythrocytic elements. A second marrow study on Mar. 21, 1941, after a period of combined therapy, revealed a similar hyperplasia but to a lesser degree.

	Bone Marrow Studies		
	Nov. 3, 1939	Oct. 21, 1940	Mar. 21, 1941
Total nucleated cells	138,000	640,000	410,000
Megakaryocytes	—	200	250
Segmented neutrophiles	15.0	20.0	21.0
Non-segmented neutrophiles	20.0	29.5	28.0
Lymphocytes	15.0	7.0	13.5
Eosinophiles	5.0	2.5	2.5
Neut. myelocytes	30.0	27.0	30.5
Eos. myelocytes	—	3.5	1.5
Plasma cells	—	1.0	2.0
Myeloblasts	—	4.5	0.5
Myelogones	15.0	5.0	0.5
Normoblasts (per	365.0	754.0	340.0
Erythroblasts 100	—	104.0	62.0
Megaloblasts W.B.C.)	15.0	10.0	21.0

Clinically the child showed general muscular improvement, gradual cessation of enuresis after several months, descent of the testicle during treatment, with retraction in intervals.

Case 3. A. P., an identical twin of *case 2*, weighed 5 lb. 1 oz. at birth. At 3 months of age he suffered from severe diarrhea and a blood transfusion was given. Otherwise he presented no outstanding symptoms until a severe anemia was noted at 10 months of age. He too was observed at the New York Hospital where therapy similar to that of *case 2* was given.

He was first seen by us on Aug. 19, 1940, at which time he presented the same picture as *case 2*, except for the absence of cryptorchidism. His blood picture at that time showed 2,050,000 erythrocytes per cu. mm.; Hb. 5.9 gm. per 100 cc. and 16 normoblasts per 100 white blood cells.

Treatment was instituted along the same lines as in *case 2*, except for the fact that in the first 2 courses he received vitamin B-6 alone, while *case 1* received pregnancy-urine hormone; he then received pregnancy-urine hormone alone while *case 2* received only vitamin B-6.

Again in this case the most marked rise in the erythrocyte level occurred during endocrine therapy alone, a less marked rise during combined treatment, and a slight rise or maintained level during vitamin therapy alone (fig. 5).

Bone-marrow studies in this case revealed the same changes as those found in *case 2*, albeit to a lesser degree.

	Bone Marrow Studies		
	Nov. 16, 1939	Oct. 21, 1940	Mar. 21, 1941
Total nucleated cells	147,200	446,000	310,000
Megakaryocytes	—	150	300
Segmented neutrophiles	6.0	23.0	34.0
Non-segmented neutrophiles	27.0	18.5	16.5
Lymphocytes	—	2.0	7.6
Neut. myelocytes	39.0	43.0	33.0
Eosinophiles	—	4.0	—
Eos. myelocytes	—	4.5	2.5
Myeloblasts	7.0	2.0	2.0
Myelogones	21.0	3.0	4.5
Normoblasts (per	540	492.0	458.0
Erythroblasts 100	—	78.0	71.5
Megaloblasts W.B.C.)	—	23.5	13.0

The clinical picture showed changes similar to those of *case 2*.

CONCLUSIONS

It may be concluded from the above findings that certain effects are produced fairly constantly in the bone-marrow cytology and in the peripheral blood in primary erythroblastic anemia following the administration of pregnancy-urine hormone and vitamin B-6. The endocrine therapy was accompanied in all 3 cases by a bone-marrow hyperplasia, especially in the erythrogenic series and also by a moderate increase in the erythrocyte level of the blood. At the same time it was noted that administration of the hormonal substance continued beyond 4 weeks seemed to produce a secondary fall in the erythrocyte level. The addition of vitamin B-6 to this line of treatment caused little variation in the direction of the effect of the hormone alone. Here it should be noted that McCullagh and Jones (7) have observed a definite rise in erythrocyte counts in patients receiving androgen therapy over long periods of time.

The administration of vitamin B-6 in large doses (50 mg. daily) caused little consistent change in the erythrocyte counts in any of the cases. Nevertheless it was not accompanied by the definite relapses which occurred on cessation of all therapy. Vilter et al. (8) observed reticulocytosis and granulocytosis on the administration of vitamin B-6 to humans with pellagra and pernicious anemia, findings which are not inconsistent with our own results.

During the period of treatment, cessation of enuresis was observed and in one case there was a temporary correction of cryptorchidism. There appeared

to be a general increase in muscular development after prolonged therapy.

These findings do not appear to offer any great clinical addition to the treatment of Cooley's anemia. Nevertheless they are offered as a possible means of therapy in Cooley's anemia for maintaining a fairly normal erythrocyte blood level after that has been reached by repeated blood transfusions.

SUMMARY

Three cases of primary erythroblastic anemia are presented. The effect of administration of pregnancy-urine hormone (prolan B), of vitamin B-6, and of the two combined, on the bone marrow and peripheral blood picture is described. The effect of these substances on the general clinical picture in Cooley's anemia is noted.

We wish to express our appreciation to Dr. W. Antopol for his invaluable advice, to Dr. Robertson of Merck and Co., Inc. Rahway, N. J., for the supply of vitamin B-6, and to Dr. Carl Smith, of the New York Hospital, for his cooperation in supplying clinical data in two of the cases presented.

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The Occurrence of Unusual Amounts of Estrogens in the Urine of Boys with Progressive Muscular Dystrophy[1]

[Muscular Dystrophy]

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IN VIEW OF RECENT reports (1, 2, 3) that large doses of vitamin E cause improvement in certain cases of progressive muscular dystrophy we have been interested in the problem of what factors might increase the demands for vitamin E or might be antagonistic to the biological action of alpha tocopherol. The suggestion has been made (4, 5) and later criticized (6) that the presence of excessive amounts of estrogenic substances may have such an effect. Without entering this controversy it suffices at the present time to state that these reports led us to study the excretion of estrogens in the urine of several young boys with typical pseudohypertrophic progressive muscular dystrophy.

Our procedure for the extraction and bioassay of estrogens was essentially that described by Cherry and Bernstein (7). A liter or less of urine from these patients, acidified by the addition of 5 cc. of concentrated HCl to each 100 cc. of urine, was boiled with a reflux condenser for 1 hour. After cooling the urine was vigorously shaken for 1 hour with an equal volume of ethyl ether which had been previously treated to remove peroxides. The ether fraction was then separated, washed several times with saline and subjected to distillation at reduced pressure to remove the ether. The residue was taken up in 5 cc. of sesame oil and injected into several castrated female mice in order to test for the presence of estrogens.

Four or five spayed mice were used to test each sample. Each mouse received 3 injections of 0.2 cc. of the extract in sesame oil at the following intervals: at 9 A.M. and 5 P.M. on the first day and at 9 A.M. on the second day. Vaginal smears were examined at 12-hour intervals starting 48 hours after the first injection and continuing for 48 hours longer. Thus far the urine from 8 boys with muscular dystrophy has been studied. In every instance full vaginal estrus was produced in the majority of a group of test mice. The criterion of estrus was the disappearance of all white cells from the smear leaving only cornified epithelial cells. Coincident with the change in the smears relaxation of the vaginal orifice and swelling of the nipples were usually noted. In some instances the mice were killed when the vaginal smears were typical of estrus in order to make histological studies of the uterus and vagina. Grossly the uteri were markedly enlarged over the resting state and appeared to be congested. Microscopically both the uterus and vagina showed the histological changes typical of true estrus.

Similar studies have been carried out on the same or somewhat larger amounts of urine obtained from normal boys of comparable age. In no instance have we obtained extracts from normal urine which produced any appreciable change in the vaginal smears of castrate female mice. Hence, although we do not as yet have figures showing the actual amounts of estrogenic material present it seems clear that boys with progressive muscular dystrophy excrete considerably greater amounts of such substances than do normal boys of corresponding age.

Since it has been found (8, 9) that certain androgens if present in sufficient amounts produce vaginal changes similar to those produced by estrogens it seemed desirable to take further steps to identify as true estrogens the substances extracted from the urines of boys with muscular dystrophy.

The usual method (10) of separating androgens and estrogens is to subject the ether extract to repeated treatment with a 10% solution of NaOH. Estrogens are taken up in the alkaline aqueous solutions while androgens remain in the ether fraction. We found that when ether extracts of urines from dystrophic patients were treated with alkali the ether fraction entirely lost the power to produce vaginal changes while material was taken over into the alkaline solution which after subsequent recovery produced typical estrus. Thus the substance which is present in unusual amounts in the urine of boys with muscu-

Received for publication September 29, 1941.

[1] This work was aided by a grant from the John and Mary R. Markle Foundation.

lar dystrophy has both the chemical behavior and biological activity of true estrogens.

Until a great deal more work has been done we are unprepared to offer any interpretation of what significance the observed increase in estrogens may have in relation to vitamin E or to the broader problem of progressive muscular dystrophy. In the published reports of numerous experiments in which estrogens have been administered to immature animals there is no indication that muscular function or metabolism is adversely affected by estrogenic excess. Possibly the increased estrogens are merely incidental to some primary abnormality which affects both muscle metabolism and the formation of estrogens.

SUMMARY

Unusually large amounts of estrogenic material have been extracted from the urine of 8 boys with typical pseudohypertrophic progressive muscular dystrophy. When injected into castrated female mice this material caused typical vaginal estrus as shown by vaginal smears and at the same time produced in uterus and vagina the histological changes which are typical of true estrus. Until more work is done no interpretation of the significance of this finding can be offered.

I wish to express my thanks to Dr. Doris H. Phelps of the Department of Obstetrics and Gynecology for assistance and many helpful suggestions in the course of this work.

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The Daily Variation in 17-Ketosteroid Excretion of Men and Women

[Ketosteroid Excretion]

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IT HAS BEEN FOUND (1) that the amount of androgen excreted in the urine of normal adults varies from day to day when determined by the Zimmermann (2) reaction. This fluctuation is approximately ±40% about a mean which is relatively constant for an individual, even over long periods of time. This finding has been recently confirmed (3). However, Callow (4) demonstrated that there is normally a nonspecific chromogenic fraction which gave a color value of about 6% of the total in a small number of urine specimens from several subjects. Talbot (5) confirmed this although he found a much higher value for this fraction in a number of instances. The question thus arises whether the daily fluctuation in total androgen output of the individual subject is accounted for by changes in the output of this nonspecific component or in the output of the specific 17-ketosteroids.

Callow (4) has used the ratio of absorption coefficients with green and violet filters E_G/E_V, to determine whether an extract is relatively pure or whether there is a good deal of contaminating chromogen. This is possible since the absorption curves for the pure hormone and for the impurities are quite different. Thus Callow found a ratio of E_G/E_V of less than 0.8 with the Spekker photometer to be consistent with reasonable purity of an extract. This is equivalent to a ratio of extinction coefficients E_G/E_V of more than 1.5, using the photoelectric colorimeter (5). This ratio, when applied to the day-to-day rise and fall of 17-ketosteroid output indicates that this change is not due to impurities (1). Forbes and Friedman (3) have approached the problem of eliminating the factor of non-specific chromogens by a mathematical equation, but find the daily variation still persists.

The introduction of Girard's reagent T (6, 7), however, makes possible the actual chemical separation of the hormonal from the non-hormonal material since the former is ketonic in nature and the latter non-ketonic. The present study has utilized this procedure to determine which fraction is responsible for the daily variations in the total 17-ketosteroid excretion.

METHODS AND MATERIALS

The entire urinary output of 2 men, aged 22 and 23 and one woman aged 25, medically normal, was collected in 48-hour batches. The urine was preserved with chloroform and kept in an ice-chest during the collection. The methods previously used (1) were followed in detail with the exception of relatively minor changes in the procedure for 17-ketosteroid determinations.[2] The changes in the technique for determining 17-ketosteroid involved the substitution of 2.5N alcoholic KOH for aqueous KOH and the use of an Evelyn photoelectric colorimeter for reading the developed color. Each series of determinations was checked by concurrently running a standard solution of androsterone in alcohol. The color of the original alcoholic urinary extract was accounted for by taking the material used in routine determination, but substituting pure alcohol for the m-dinitrobenzene solution. This mixture was then added to the diluted chemical blank and the resulting reading on the galvanometer recorded. The amount in terms of milligrams was subtracted from the total obtained by the completed reaction for the sample. The method for the separation with Girard's reagent T of the ketonic from the non-ketonic material was that outlined by Talbot (7).[3]

Received for publication October 22, 1941.

[1] Aided by a grant for teaching and research in neurology, The Rockefeller Foundation, and by a gift for research in human sex biology from Albert Lasker.

[2] It should be mentioned that with the 5% concentration of HCl used in the above method, the destruction of dehydroisoandrosterone during hydrolysis is only 0–15%, unlike the 30% with acid concentrations of about 15% used by Talbot (5).

[3] There is a constant loss of about 10–15% of the 17-ketosteroids during this procedure, probably into the non-ketonic fraction (7).

RESULTS

The daily fluctuation in total androgen or 17-ketosteroid output was found to be due to variations in the true hormonal or ketonic fraction of the urine (fig. 1–3). The non-ketonic, non-hormonal fraction usually was found to be quite small in amount. The total 17-ketosteroid output per 24 hours varied from 6 mg. to 14.2 mg. (mean 11.2 mg.) and from 10.1 mg. to 17.3 mg. (mean 15.0 mg.) in the 2 males, from 6.9 mg. to 12.2 mg. (mean 10.2 mg.) in the female. The corresponding ketonic fractions showed values per 24 hours closely parallel to the total ranging from 4.1 mg. to 12.8 mg. (mean 10.2 mg.) and from 8.7 mg. to 15.6 mg. (mean 13.1 mg.) in the men respectively and from 4.8 mg. to 12.2 mg. (mean 9.0 mg.) in the woman. The non-ketonic fraction in most instances represents the difference between the total and the ketonic fraction, plus or minus a few tenths of a milligram. The actual values of this latter fraction per 24 hours ranged from 0.3 mg. to 1.5 mg. (mean 0.7 mg.) and from 0.7 mg. to 2.4 mg. (mean 1.3 mg.) in the men; from 0.5 mg. to 1.6 mg. (mean 1.1 mg.) in the woman. Correlation with E_G/E_V, the ratio of extinction coefficients with green and violet filters, showed that all specimens in this study fell well within the limits required by Callow to indicate sufficient purity of the extract to insure a reasonably close approximation to the actual hormone content.

DISCUSSION AND CONCLUSIONS

The daily fluctuation in 17-ketosteroid output of normal men and women as determined by the Zimmermann reaction was found to be present even after the true hormonal, or ketonic, fraction was separated by Girard's reagent T. The non-ketonic fraction did not vary enough in amount to affect the total significantly. The degree of variation in the hormone output from day to day thus makes the interpretation of small changes in 17-ketosteroid excretion difficult unless enough specimens have been assayed to establish a mean excretion from which to evaluate change.

The small proportion of impurities in normal urine as indicated by the Girard's reagent separation is also reflected in the ratio of the extinction coefficients with the green and violet filters, E_G/E_V. The use of Girard's reagent then would appear to be necessary only for those instances in which this ratio indicates an excess of non-ketonic material. This has been

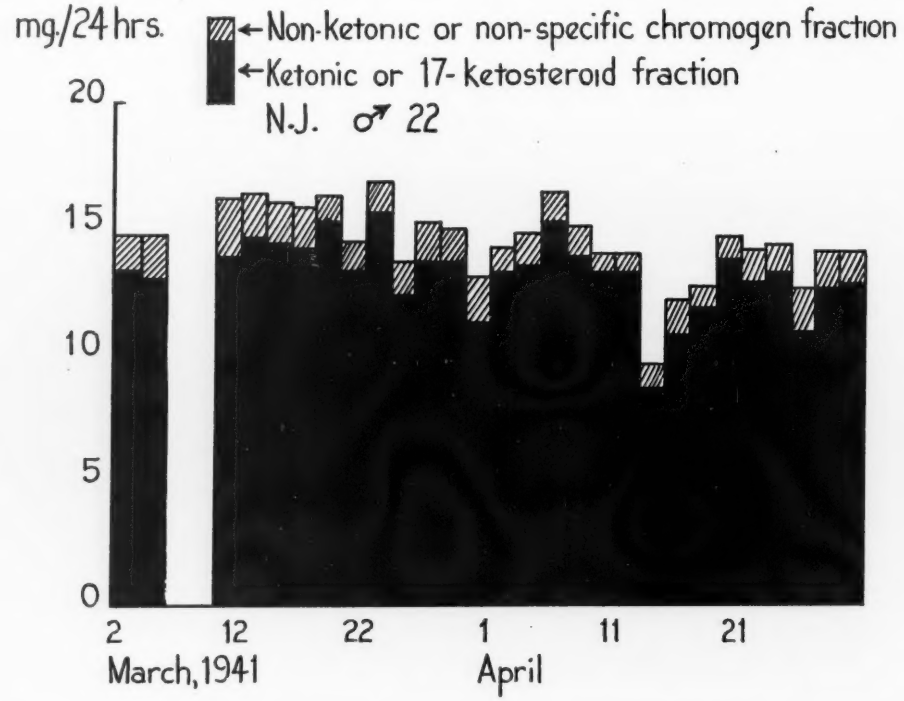

Fig. 1. Graph showing the values of the ketonic and non-ketonic fractions of the 48-hour urinary 17-ketosteroid output as determined by the Zimmermann reaction, of a normal man, aged 22 years, over a 2-month period.

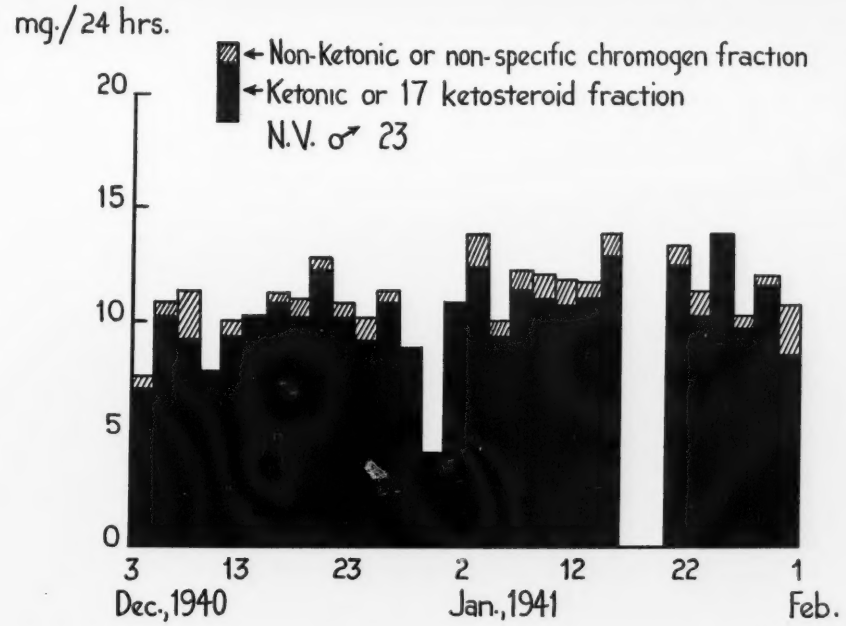

Fig. 2. Graph showing the values of the ketonic and non-ketonic fractions of the 48-hour urinary 17-ketosteroid output as determined by the Zimmermann reaction, of a normal man, aged 23 years, over a 2-month period.

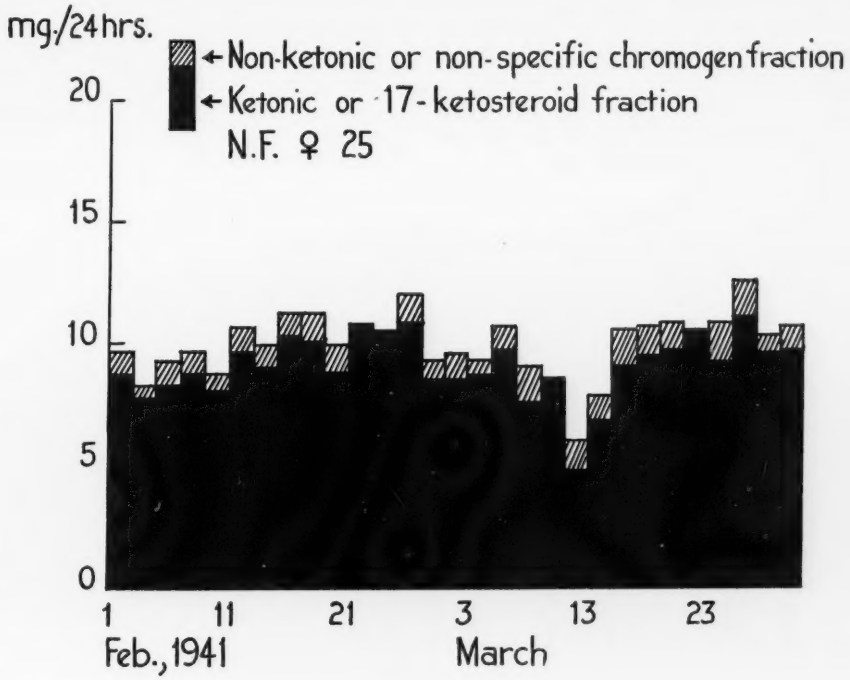

Fig. 3. Graph showing the values of the ketonic and non-ketonic fractions of the 48-hour urinary 17 ketosteroid output as determined by the Zimmermann reaction, of a normal woman, aged 25 years, over a 2-month period.

checked in a number of specimens from patients with various conditions.

The cause of the fluctuation in ketosteroid output by the healthy person is as yet unexplained. Forbes and Friedman (3) have obtained interesting data on the effect of operation and sickness indicating that the output is readily influenced by changes in the physiological status of the patient. But the determination of just what levels should be considered beyond the range of normal is difficult in view of this broad range of normal, unless the determination in question is well outside this range. It thus should be emphasized again that if the deviation from normal is only slight, enough baseline determinations are necessary to establish a mean for the individual from which to judge the significance of the change.

The author is indebted to Dr. Oskar Wintersteiner, Department of Biochemistry, for his valued advice and to Miss Helen Brunn for her technical assistance.

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The Relation of Arteriosclerosis to Diabetic Neuritis of the Lower Extremities

[Diabetic Neuritis]

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THE PATHOGENESIS OF NEURITIS in patients with diabetes mellitus is still the subject of controversy. This centers about the relative rôles played in the production of the neuritis by ischemia on the one hand and some purely hypothetical, perhaps nutritional, factor inherent in diabetes on the other. Although clinical and pathological observations seem to indicate that the ischemic element is by far the more important, the exact part that the ischemia plays either alone or in combination with other factors has not been adequately studied. The present investigation was undertaken in an attempt to clarify this point.

The clinical data presented here is based on a study of 150 patients from the wards and out-patient department of the Peter Bent Brigham Hospital. These patients fall into three groups: *a*) Sixty-five cases of diabetes mellitus, *b*) 80 cases of generalized arteriosclerosis, and *c*) 5 cases of neuritis associated with a locally deficient blood supply. The history and the neurological, clinical and laboratory examinations have been studied in an effort to determine the importance of arteriosclerosis and the resultant ischemia in the production of neuritis.

It has been found convenient to divide the clinical cases studied into five categories according to the nature and manifestations of the disease process. In the first group are young, uncontrolled diabetic patients with signs and symptoms of peripheral neuritis but no evidence of circulatory impairment. The second group consists of uncontrolled diabetic patients with signs and symptoms of peripheral neuritis and circulatory impairment. The third group comprises those patients in whom the diabetes was controlled, but who had signs and symptoms of peripheral neuritis associated with generalized arteriosclerosis and evidence of a deficient blood supply to the lower extremities. The fourth group of patients, who were nondiabetic, had evidence of generalized arteriosclerosis, manifestations of peripheral neuritis, and evidence of a deficient blood supply to the lower extremities. The fifth group is composed of patients, also nondiabetic, with evidence of peripheral neuritis associated with circulatory impairment from some cause other than arteriosclerosis.

At the start it is essential to list the criteria used in this study. As far as could be determined and unless otherwise stated, the patients studied did not have causes other than diabetes and arteriosclerosis for their symptoms of peripheral neuritis. The diets were all considered adequate, and they were checked at least once a month by the hospital dietitian. None of the patients used alcohol to excess, or presented any evidence that a toxic factor played more than an insignificant rôle. There was no serological or clinical evidence of syphilis in any of the cases studied.

According to Cobb and Coggeshall (2) peripheral neuritis is "a painful degenerative process in any part of the peripheral neuron causing a functional loss, which, according to the anatomy involved, may be sensory, motor or mixed." Therefore, before any patient was judged to have peripheral neuritis, a majority of the following findings had to be present.

a) Sensory changes including hypesthesia to pin prick, cotton wool, heat or cold; *b*) diminished reflexes or definite motor impairment; *c*) pains which might include paresthesias. Though occasionally dull and continuous, the pains were usually sharp and shooting in character, and ill-defined except on rare occasions when they were limited to the course of a single nerve. Numbness, tingling, prickling, burning or coldness were the characteristic paresthesias, often described by the patients in bizarre terms, such as "a sensation as if I had thick crepe soles on my shoes."

If the diagnosis of generalized arteriosclerosis was to be made, the patient had to have several of the following symptoms or signs: a high pulse pressure, anginal symptoms, definitely sclerotic arteries whether by palpation or as observed by roentgen examination, and retinal changes suggestive of arteriosclerosis. The patient was judged to have a deficient blood

Received for publication September 9, 1941.

TABLE 1. DIABETIC PATIENTS NOT IN CONTROL HAVING SYMPTOMS OF PERIPHERAL NEURITIS AND CIRCULATORY DEFICIENCY

Age	Evidence for		Control of diabetes
	Peripheral neuritis	Arteriosclerosis	
65	sensory change pain	Generalized D.P.[1] present	out of control 6 mo.
69	sensory change pain	Generalized D.P. o Left + Right	out of control 2 yrs.
70	pain reflexes diminished sensory change	Generalized D.P. absent	out of control unknown period
53	pain sensory change reflexes diminished	Generalized D.P. o Left + Right	out of control 3 mos.
57	pain sensory change reflexes diminished	Generalized D.P. absent	out of control yrs.
54	pain sensory change	Generalized D.P. present Int. claud.	out of control yrs.
60	reflexes diminished sensory change pain	Generalized D.P. absent	out of control 1 yr.

[1] Dorsalis pedis.

supply to the lower extremities if he had evidence of coldness in one of the extremities as compared with the other, symptoms of intermittent claudication, or an absent or diminished pulsation in the dorsalis pedis or posterior tibial arteries. The lower extremities were found to be more often involved and easier to study than the upper extremities.

It is well to remember that in the group dealt with here, the usual variations inherent in sensory examinations and the difficulties in making certain of accurate localization and description were enhanced by the presence of the cerebral arteriosclerosis which usually accompanied the more general type of arteriosclerosis. Accurate description was further impeded by language difficulties. In addition, ankle jerks are not infrequently absent in elderly poeple. The findings here are expressed, therefore, in terms of the most consistent results obtained.

There were but 2 cases studied which fell into *group a*, namely young patients with uncontrolled diabetes mellitus having symptoms of neuritis. These patients, aged 22 and 30, had diabetes for 4 and 10 years respectively. Their diabetes was not controlled at the time they were first examined and signs and symptoms of peripheral neuritis were present including hypesthesia, loss of ankle jerks and sharp shooting pains. Both had no symptoms or signs of neuritis after the blood sugar was controlled with adequate diabetic therapy. In the second patient, dietary factors may have played a significant rôle. Although the series presented here is small, the literature reveals more instances of young patients in whom the neuritis disappeared after diabetes was controlled. Jordan (5) reported 34 cases of this type, and remarked that relief was so prompt after diabetic treatment was started that no other therapy was even considered. Woltman and Wilder (12) stated that if one can exclude from consideration the pains of acidosis which promptly disappear when the acidosis is brought under control, young persons with diabetes practically never complain of pain, paresthesias or other neurological symptoms.

The second group included 7 cases of unregulated diabetes with circulatory deficiency and neuritic manifestations. The ages varied between 53 and 70 years averaging 61 years. All of the cases in this group

TABLE 2. DIABETIC PATIENTS IN CONTROL HAVING SYMPTOMS OF PERIPHERAL NEURITIS AND CIRCULATORY DEFICIENCY

Age	Evidence for		Control of diabetes
	Peripheral neuritis	Arteriosclerosis	
64	pain sensory changes reflexes diminished	Generalized D.P.[1] absent Int. claud.	in control no effect
65	pain sensory changes reflexes diminished	Generalized D.P. present	in control
63	pain sensory changes reflexes diminished	Generalized D.P. present	in control
48	pain reflexes diminished	Generalized D.P. present Int. claud.	in control 10 years
63	pain sensory changes	Generalized D.P. present	in control 11 years
73	pain sensory changes reflexes diminished	Generalized D.P. present	in control 17 yrs.
55	pain sensory changes	Generalized D.P. present	in control 11 years
68	pain sensory changes reflexes diminished	Generalized D.P. absent	in control 20 years
71	pain sensory changes reflexes diminished	Generalized D.P. absent Int. claud.	in and out of control 2 years
67	pain sensory changes	Generalized D.P. present	in control
69	pain sensory changes reflexes diminished	Generalized D.P. present Int. claud.	in control 12 years
67	pain reflexes diminished	Generalized D.P. present	in control 11 years

[1] Dorsalis pedis.

had gangrene involving the lower extremities (table 1). Likewise, they all had varying manifestations of neuritis and evidence of generalized arteriosclerosis. In 6 cases the dorsalis pedis was absent in the leg involved by the gangrene, and in 2 cases, the dorsalis pedis was absent in the leg not gangrenous. In all of these cases the diabetes mellitus had been out of control before the onset of the gangrene.

In the third group were included the cases who had controlled diabetes, evidence of circulatory deficiency, and peripheral neuritis. Sixty-five consecutive diabetic patients were examined of whom 12, or 18.5%, fell into this group (table 2). Their ages varied between 48 and 73 years, the average being 64 years. All the patients except one had controlled their diabetes satisfactorily for many years and had developed the symptoms of neuritis despite the fact that the diabetes was under control. One patient, age 64, had evidence of peripheral neuritis while his diabetes was uncontrolled, and the establishment of diabetic control had no effect on the symptoms and signs of the peripheral neuritis. All cases except one had definite evidence of generalized arteriosclerosis. Five of the 12 cases had absence of dorsalis pedis in one or both legs. Clinically the peripheral neuritis was generally more severe in those cases who did not have a palpable dorsalis pedis. Four cases, in 2 of which there was absent dorsalis pedis, had intermittent claudication as part of their symptom complex. Two cases had unilateral neuritic involvement.

TABLE 3. NONDIABETIC PATIENTS HAVING SYMPTOMS OF PERIPHERAL NEURITIS AND CIRCULATORY DEFICIENCY

Age	Evidence for	
	Peripheral neuritis	Arterioclerosis
68	pain sensory changes reflexes diminished	generalized D.P.[1] present Int. claud.
66	pain sensory changes	generalized D.P. absent
58	pain sensory changes reflexes diminished	generalized D.P. present
66	pain reflexes diminished	generalized D.P. o Right + Left
60	pain sensory changes reflexes diminished	generalized D.P. present unilateral
83	pain sensory changes reflexes diminished	generalized Int. claud.
62	pain sensory changes	generalized D.P. present

[1] Dorsalis pedis.

TABLE 4. PATIENTS HAVING CIRCULATORY DEFICIENCY OTHER THAN ARTERIOSCLEROSIS AND HAVING PERIPHERAL NEURITIS

Age	Evidence for peripheral neuritis	Nature of circulatory deficiency
64	pain sensory change reflexes diminished	embolus to fem. artery of R. leg.
40	pain reflexes diminished sensory change	embolus into brachial and radial
42	pain sensory change reflexes diminished	polycythemia
47	pain sensory change	Buerger's, unilateral
54	pain sensory change	rider embolus

Jordan (5) stated that the pain in diabetic neuritis is usually more severe at night, but we found no evidence of this.

In the fourth group were patients with generalized arteriosclerosis who had evidence of peripheral neuritis, but did not have diabetes mellitus. This is a group often speculated about, but rarely studied probably because of the inherent difficulties involved in studying individuals with generalized arteriosclerosis. We investigated 80 cases of generalized arteriosclerosis and found that 7 cases, or 8%, had symptoms of peripheral neuritis (table 3). The ages of the patients varied from 58 to 83 years, the average age being 67, three years more than the average in the diabetic group. All of the cases presented had definite evidence of arteriosclerosis and of peripheral neuritis. In one instance, age 60, the symptoms were much more pronounced on one side than on the other.

In the fifth group (table 4) there were 4 patients with a deficient blood supply to one of their extremities due to some cause other than arteriosclerosis. All of these patients had definite evidence of peripheral neuritis. In the patient 47 years of age however, the situation was complicated by the fact that in Buerger's disease the neuritis may be due to direct involvement of the nerve rather than to indirect involvement through interference with its blood supply. In pathological specimens from cases of Buerger's disease, often the nerve is found to be bound down along with the artery.

DISCUSSION

The relationship between ischemia and peripheral neuritis has only recently been stressed. It is a well known clinical fact that if a tourniquet is applied to an extremity and the circulation occluded, symptoms and signs of peripheral neuritis are soon apparent.

Fetterman and Spitler (3) presented evidence to show that under the following clinical conditions, damage to peripheral nerves occurs because of vascular disease: *a*) trauma, *b*) embolism, *c*) thromboangiitis obliterans, *d*) periarteritis nodosa, *e*) syphilis, and *f*) polycythemia vera.

Hassin (4) stated that when periarteritis is confined to the lower extremities, the clinical picture may be that of a typical polyneuritis. Any peripheral nerve may be involved, with the blood vessels of the nerves containing nodular thickenings which may be followed down to the final ramifications. McKenchie and Allen (7) in a study of 100 cases of sudden arterial occlusion found that when such sudden occlusion does not lead to gangrene, the symptoms due to this occlusion may merge imperceptibly into those of ischemic neuritis. Barker and Baker (1) found that in cases of ischemic neuritis, pathologic examination showed perineural and intraneural fibrosis as well as patchy loss of myelin sheath. Likewise in the literature on the other vascular diseases, which Fetterman and Spitler list as causes of neuritis (3), evidence can be found to corroborate these statements. Even in the small number of cases presented here, there is ample evidence that signs and symptoms of peripheral neuritis may follow ischemia of the extremities.

The results of this study indicate that signs and symptoms similar to those occurring in other types of ischemic neuritis may occur in patients with generalized arteriosclerosis. Pearson (8) found that there was a slight diminution in sensibility over the lower extremities in older individuals which became more noticeable decade by decade and might be pronounced after the age of 50. However, Jordan (5) stated that "evidence against the theory that arteriosclerosis is the chief cause of diabetic neuritis is found in the relative rarity of neuritis in elderly nondiabetic patients with arteriosclerosis. In 10 cases in patients over 70 years of age, there were no neuritic symptoms and the knee jerks were normal." Likewise, Wilder (11) inquired as to why, if arteriosclerosis is the principal cause of neuritis in diabetes, one does not encounter neuritis more frequently in nondiabetic patients with obliterating arteriosclerosis in whom the circulation is impaired. As we have already stated, the results obtained in our study of 80 patients revealed that peripheral neuritis is not as rare an occurrence in patients with arteriosclerosis as has been believed. In these 80 cases, all had evidence of generalized arteriosclerosis, and 7 patients, or 8%, had definite evidence of peripheral neuritis. This percentage is not insignificant when one considers that Woltman and Wilder (12) found peripheral pain in only 10% of 2,000 consecutive cases of diabetes.

Priestly (9) found that nerves nourished by arteriosclerotic arteries showed definite Wallerian degeneration and fibrosis. These changes were more pronounced in the distal portion of the nerve than in the proximal portion and appeared directly proportional to the degree of arteriosclerotic changes found in the vessels. This suggested to Priestly that ischemia was the fundamental etiologic factor in the production of degeneration. It becomes evident, therefore, that arteriosclerosis alone may produce neuritic changes indistinguishable from the other types of ischemic neuritis and also indistinguishable from diabetic neuritis.

The importance of arteriosclerotic changes in the production of diabetic neuritis is a much debated question. Since 1864, when Marechal de Calvi pointed out that diabetes was the cause rather than the result of diabetic neuritis (5), various explanations have been given for the presence of neuritis in diabetes. Jordan (5) mentioned that neurologic changes in diabetes have been attributed to: *a*) excess of sugar, *b*) cachexia, *c*) an unknown toxin due to the diabetic condition, and *d*) increase in cholesterol, with vitamin deficiency always to be considered as a possible complicating factor in any of these conditions. Although the rôle of arteriosclerosis has always been mentioned in discussions of diabetic neuritis, its importance in the production of neuritis is not established. The diabetic neuritis studied here is the type most commonly seen at the present time which seldom appears before the age of 40, is not related to the severity of the diabetes or to the dosage of insulin required for control, and shows a marked predilection for the lower extremities. This type of diabetic neuritis is to be differentiated from the more infrequent and less clearly understood 'subjective' diabetic neuritis of femoral distribution. It should likewise be differentiated from 'diabetic tabes' which includes those patients having a gradual loss of position sense and reflexes in the legs with no cause for this other than diabetes. In the cases studied here, all of the patients with uncontrolled diabetes mellitus, had evidence of generalized arteriosclerosis. Furthermore the neuritis found in those patients with diabetes was indistinguishable from the neuritis found in those patients with arteriosclerosis alone. Two of the patients with a combination of neuritis and diabetes had predominantly unilateral involvement, similar in all respects to that found in one case of arteriosclerosis with unilateral involvement predominating. Kraus (6) likewise found that the signs in diabetic neuritis may predominate on one side more than the other. The fact that one does find diabetic neuritis in which the involvement is chiefly unilateral is evidence in favor of a local vascular lesion rather than a generalized diabetic factor being

considered the causative agent. Jordan (5) reported that loss of sensation in diabetic neuritis, when present, increases progressively from the thighs down to the feet, but that its distribution is usually patchy. This patchy distribution also seems to favor a local vascular lesion rather than a generalized factor as responsible for the neuritis.

Pathologically, the reason for this is clear. Woltman and Wilder (12) found that the most significant lesion in diabetes was in the nerve trunk. There was arteriosclerosis of the nutrient vessels to the nerves, and these patchy areas were more marked distally. The pathological description of subjects with diabetes coincided with the description of the arteriosclerotic and senile neuritis observed in patients free of diabetes. This led these investigators to the conclusion that "arteriosclerosis of the nutrient vessels and nerves and the ischemia resulting therefrom probably played a leading part in the production of diabetic neuritis." Warren (10) studied nerve specimens from legs amputated for diabetic gangrene and found sclerosis of the intra-neural arterioles and occasional myelin degeneration.

Although final and absolute proof for the assumption that arteriosclerosis and the resultant ischemia are the only cause for the symptoms of diabetic neuritis is lacking, multiple reasons may be advanced for believing that these two factors are the chief cause of these symptoms. It has been shown that symptoms and signs of peripheral neuritis may be due to a deficient blood supply. The symptoms and signs of the peripheral neuritis are found in significant numbers of patients with generalized arteriosclerosis, and they are similar in all respects to the symptoms and signs of other forms of ischemic neuritis and diabetic neuritis. Pathologically, there is a striking similarity between the lesion found in the neuritis associated with arteriosclerosis and that found in diabetic neuritis.

CONCLUSIONS

A study of 150 patients with diabetes mellitus or with circulatory disturbances was made. There were 65 diabetic cases, 80 cases of generalized arteriosclerosis, and 5 cases with deficient blood supply to the extremities not due to arteriosclerosis or diabetes.

In this study evidence of peripheral neuritis was found in 18% of the cases of diabetes, in 8% of the patients with generalized arteriosclerosis, without diabetes, and in all the cases with grossly deficient blood supply to the extremities.

Symptoms and signs of peripheral neuritis may be found in patients with a deficient blood supply to the extremities, regardless of the cause of this deficiency.

Symptoms and signs of peripheral neuritis may be found in patients with generalized arteriosclerosis, similar in all respects to those of ischemic neuritis and diabetic neuritis.

Arteriosclerosis and the resultant ischemia is a major cause in the production of diabetic neuritis.

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The Effects of Large Doses of Intravenous Insulin in Psychotic Nondiabetic Patients

{[Insulin in Psychosis]}

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The advent of the insulin shock treatment of schizophrenia, introduced by Sakel (1), has furnished an unexcelled opportunity to increase our knowledge of certain phases of carbohydrate metabolism and of the pharmacodynamics of insulin. A number of studies have been made of blood sugar and lactate during prolonged hypoglycemic coma and convulsions produced by intramuscular injections of insulin (2–6). In Sakel's treatment several hours elapse before the onset of central nervous system irritation, and varying degrees of sensitivity to insulin are manifested. This variability has also appeared among the schizophrenic patients we have treated with insulin; some failed to display irritability of the central nervous system, even though 500 units of insulin was injected intramuscularly.[1]

It has been our desire to accelerate the onset of hypoglycemia and irritation of the central nervous system. Failure to accomplish this by massive intramuscular doses of insulin has led us to administer it intravenously. Some effects of intravenous insulin were first described by Lyman et al. (7) in 1923. Three other reports have appeared since then (8, 9, 10). Our observations are instructive with regard to the effects of intravenously administered insulin on nondiabetic individuals. The clinical status of the treated patients and the bearing of these experiments on schizophrenia therapy will be reported later.

Received for publication September 6, 1941.

[1] Three of the patients (*A.F.*, *C.H.* and *H.P.*) were receiving large doses of intramuscular insulin (500, 320, 320 u) at the time we began this study. Blood sugar and lactate were followed in each subject during two treatments. The capillary blood sugar did not fall below 21 mg. % during the approximately 4 hours in which observations were made. In all cases the blood sugar reached a lower level within a shorter interval of time during the second experiment performed 48 hours later. No consistent changes in the lactate concentration were observed. In only one patient were there symptoms of central nervous system irritation (sugar 21 mg.% lactate 17 mg.%).

METHODS

Seven schizophrenic male patients of the Metropolitan State Hospital, Waltham, Massachusetts, and 4 female patients (3 schizophrenics and 1 chronic manic) from the Norwich State Hospital, Norwich, Connecticut, were used as subjects. They were all ambulatory and in sufficiently good physical condition to be engaged in some form of outdoor activity. A brief description of the patients is appended. They were on a routine hospital diet that was slightly high in carbohydrates. Twice weekly, Monday and Wednesday, the subjects were brought to the wards in a postabsorptive state at approximately 6:30 A.M. After resting in their beds for some 30 minutes, a blood sample was obtained for sugar and lactate determinations. Insulin[2] was then administered intravenously.

Samples of capillary blood were obtained 3 minutes after the injection of insulin and at various intervals thereafter for a period of 1 hour and in some cases for 2 hours. The period of hypoglycemia was terminated routinely by giving the patients a 50% solution of sucrose in coffee. The blood sugars were determined by the modified Folin-Malmros micromethod (11) and the blood lactate by the method of Edwards (12).

The criteria employed in designating the various stages of developing coma are illustrated in figure 1. Blood pressure and pulse rates are also shown.

RESULTS

Preliminary studies showed that 3 u of insulin given intravenously will appreciably lower the blood sugar of normal men and induce restlessness, perspiration, palpitation and dizziness. We therefore approached intravenous treatment of the patients with

[2] Insulin, amorphous type, Eli Lilly & Company, Indianapolis, Indiana.

extreme caution; the initial doses were 5, 8 and 10 u. When these failed to bring about hypoglycemic symptoms, the doses were first doubled and then rapidly increased until we were giving 160 u. In single studies made on each of 4 females, large doses were used, one patient receiving 360 u. At present, 500 or more u are frequently given after a preliminary trial with a small dose or doses.

Blood sugar concentrations in the male patients during the period of observation previous to and following the insulin injections are shown in table 1. Before discussing the results of intravenous treatment, it should be noted that 5 of the 7 male subjects had had previous insulin therapy; the exceptions were *B.G.* and *J.C.*, who were started on 30 u. Their dose was gradually increased to 90 and 70 u respectively. The blood lactate levels for all of the males are shown in table 2.

There are several characteristic features to be found in all of our observations. Immediately following the insulin injection there was a hyperglycemic response suggesting the presence of an impurity in the insulin. The lowest level of sugar was usually reached in approximately 30 minutes, regardless of the dose employed. Perspiration appeared at about the same time. The third feature was a fluctuating blood sugar level in which elevations and depressions were followed with another elevation, and so on.

Figure 2 illustrates the changes in blood sugar in *A.F.*, who received doses of insulin ranging from 3.4 to 160 u. These curves evaluate directly the response of the blood sugar to the presence of exogenous insulin. For discussion the curves were arbitrarily divided into 2 groups (3.4 to 70 u and 100 to 160 u). If the greatest falls in the blood sugar concentrations following insulin are averaged, values of 63 and 72 mg.% for the two groups respectively are obtained. There was some overlapping of these average points since a fall of 73 mg.% was observed with 35 u compared to a value of 79 mg.% with 120 u. The greatest fall observed in the males was 86 mg.% in *A.F.* with 140 units. An increase in the dosage of insulin did not necessarily produce a more rapid or sustained response. In *A.F.* 20 u was as efficacious in lowering and keeping the blood sugar down as was 100 or 160 u.

The changes in the blood sugar concentrations in the patient *A.F.* are in general similar to the changes observed in the other subjects. Two of these patients, however, show some interesting differences. *J.R.* had shown the lowest levels of blood sugar at approximately 30 minutes following injection of insulin up to 140 u, but when given 160 u very little change appeared in the sugar levels until 80 minutes had elapsed. Unfortunately we were unable to repeat this experiment. In the second experiment a considerably

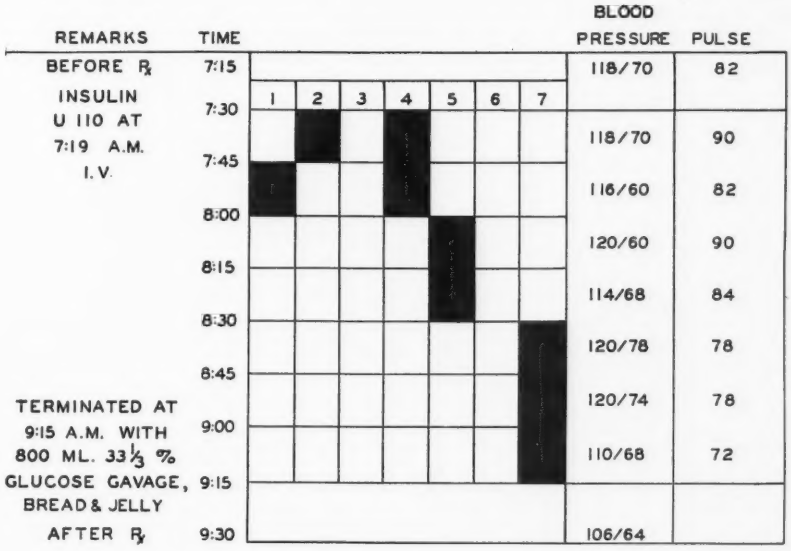

Fig. 1. Pattern of reactivity of a patient (*T.M.*) following intravenous insulin. Key: *Column 1*, hunger. *Column 2*, restlessness, anxiety, headache. *Column 3*, fatigue, somnolence. *Column 4*, sweating, dermatome distribution. *Column 5*, exophthalmos, facial spasms, sensory disturbances, twitching of facial muscles. *Column 6*, generalized tonic-clonic convulsions. *Column 7*, coma, generalized persistent decerebrate rigidity.

smaller hypoglycemic effect was shown by C.H. than in the first, even with a larger dosage of insulin in each case. Blood lactate levels showed no consistent changes, remaining at essentially normal levels unless the subject was active.

before the lowest level was observed instead of an average of 28 minutes observed in the college students. In addition, the return of the blood sugar to basal values was considerably delayed in the schizophrenics (fig. 3). The blood sugar of the fourth patient, J.R., was not appreciably altered by the presence of exogenous insulin.

TABLE 1. BLOOD SUGAR OF SCHIZOPHRENIC PATIENTS FOLLOWING INTRAVENOUS ADMINISTRATION OF INSULIN

Date	Insulin	Basal	Time in minutes, after insulin intravenously																				
			3	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
	U		*Blood sugar values, in mg. per 100 cc. of blood*																				
A.F. 6/24	10	112	111	90		61			44			53		46		61						66		
6/26	20	85	107		58		29		26		29				29			32						
7/1	25	104	110	110			59			40		42			43			54						
7/3	35	100	111		97		43		27		37													
7/24	50	108	122	130		91		61		52		68		62				66						
7/29	70	109	129	129		112		83		49		67				65								
7/31	100	108	122	113		97		49		36			50				56							
8/5	120	120	124	115		82		41			51			51			53							
8/7	140	98	111	12		67		29			53					49			64					
8/12	160	100	112	97		77		30				44						43						51
8/16	3.4	110	121	86		73			53				91											
C.H. 6/24	8	100	90	86		82			78			83		163		86						109		
6/26	16	71	88		84		68		55		61				52			57						
7/1	21	149	87	99			77			64		59			57			69						
7/3	30	89	64		91		85		47		44			33			49							
H.P. 6/24	5	101	97	94		92			90			85		84		102								
6/26	10	80	96		92		89		76		63				63			71						
7/1	15	94	99	104			102			89		78			66			61						
7/3	20	87	110		111		91		78		66			43			78							
J.R. 7/24	50	113	130	135		82		51		56		78		68				74						
7/29	70	117	140	135		65		39		74		70				66								
7/31	100	118		131		82				52			66				61							
8/5	120	103	125	130		97		62			41			64			58							
8/7	140	110	82	227		101		42			53					61			46					
8/12	160	90	98	125		119		100				75						43						48
8/16	3.2	99	113	91		103			102				107											
B.G. 7/31	30	120	115	141		70		42		47			54				60							
8/5	60	115	119	112		64		33			53			53			44							
8/7	70	110	120	104		66		41			37					44			40					
8/12	90	100	105	51		60		21				28						37						49
8/16	3.3	96	101	85		66			62				82											
J.C. 7/31	30	93	104	102		49		41		50			44				55							
8/5	40	108	117	70		35		39			45			55			43							
8/7	50	111	122	69		47		41			86					42			90					
8/12	70	95	128	90		43		21				50						63						20
8/16	3.7	97	101	71		68			58				84											
A.G. 7/24	20	103	111	122		104		86		72				63										
7/29	30	100	114	127		105		73		49		45				51								

The blood sugar in 4 female patients receiving intravenous insulin only once fell to lower levels than was noted for any of the males. In C.F. it fell to 12 mg.% with 360 U (table 3).

Through the courtesy of Dr. Clark Heath (13), we have compared his data on blood sugar responses to an intravenously administered insulin dosage of 0.05 units per kg. in college students with those in 4 of our patients receiving the same doses. Three of our schizophrenics exhibited a delayed response to intravenous insulin, as shown by the 35 minute period elapsing

DISCUSSION

The response to intravenous insulin was similar to that of intramuscular insulin, no ill effects were observed. Essentially, the symptoms following insulin administered intravenously are similar to those following intramuscular injections. The pattern of reactivity was a neuropsychiatric syndrome involving progressive functional decortication and decerebra-

TABLE 2. BLOOD LACTATE OF SCHIZOPHRENIC PATIENTS FOLLOWING INTRAVENOUS ADMINISTRATION OF INSULIN

Date	Insulin	Basal	Time in minutes, after insulin intravenously																				
			3	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
	U		*Blood lactate values, in mg. per 100 cc. of blood*																				
A.F. 6/24	10	21	17			21						19				21						14		
6/26	20	13	24			19						17						21						
7/1	25	12					19					18						10						
7/3	35	21			29				21					22										
7/24	50	18				19						23						21						
7/29	70	26				23				26						20								
7/31	100	16				21				22			22				22							
8/5	120	16		17													18							
8/7	140	10						18											16					
8/12	160	10																						9
8/16	3.4	10											10											
C.H. 6/24	8	11	20													10						17		
6/26	16	14	16				13								11			15						
7/1	21	10					9					12						9						
7/3	30	18					16				12						13							
H.P. 6/24	5	11	20						12			13				16						9		
6/26	10		39				20				16							18						
7/1	15	12					15					10						12						
7/3	20	17					17				13						11							
J.R. 7/24	50	16				26				23		26						23						
7/29	70	14				19				20						20								
7/31	100																							
8/5	120	19															20							
8/7	140	17						16											19					
8/12	160	18				9																		20
8/16	3.2																							
B.G. 7/31	30	14											21				13							
8/5	60	18																						
8/7	70	17						21											24					
8/12	90	19						16																21
8/16	3.3																							
J.C. 7/31	30	12											18				21							
8/5	40	13		17													22							
8/7	50	17						21											21					
8/12	70	11																						20
8/16	3.7																							
A.G. 7/24	20	14				13								13										
7/29	30	13				17				16														

tion, leaving the body to function primarily on a low medullary level in the terminal phases. This progression is illustrated in figure 3. *Phases* 2, 3, 4, 5 are practically universal reactions. *Phase* 7 was infrequently observed except when patients were given large doses of insulin. The convulsion stage (*phase* 6) was least common. Patients who displayed much perspiration passed from *phases* 3, 4, 5 into 7 without 6, while those patients who had intensive myoclonic twitches usually did not go into *phase* 7, except after long intervals. However, it must be emphasized that the whole picture was an episodic one with flashes of consciousness with and without amnesia mingled with periods of stupor deepening into coma. The coma produced by intravenous insulin is in general much quieter than that induced by intramuscular insulin. Recovery was in many cases spontaneous after some two hours, and no recurrences of coma or convulsions were observed, regardless of whether the hypoglycemic state was relieved spontaneously or by the ingestion of sucrose. The quality, intensity, sequence and duration of the reactions may vary not only in different patients, but also in the same patient on different days. The blood pressure showed slight changes, while in many cases the pulse rate either remained unchanged or decreased.

TABLE 3. BLOOD SUGAR IN FEMALE PSYCHOTIC PATIENTS FOLLOWING THE INTRAVENOUS ADMINISTRATION OF INSULIN

Subject	U of Insulin	Basal	Blood Sugar mg. %					
			15	35	50	75	100	120
B.S.	160	116	70	15	32	20	26	30
A.W.	340	114	108	26	29	32	30	24
O.M.	120	93	87	32	19	21	19	18
C.F.	360	125	89	40	34	38	24	12

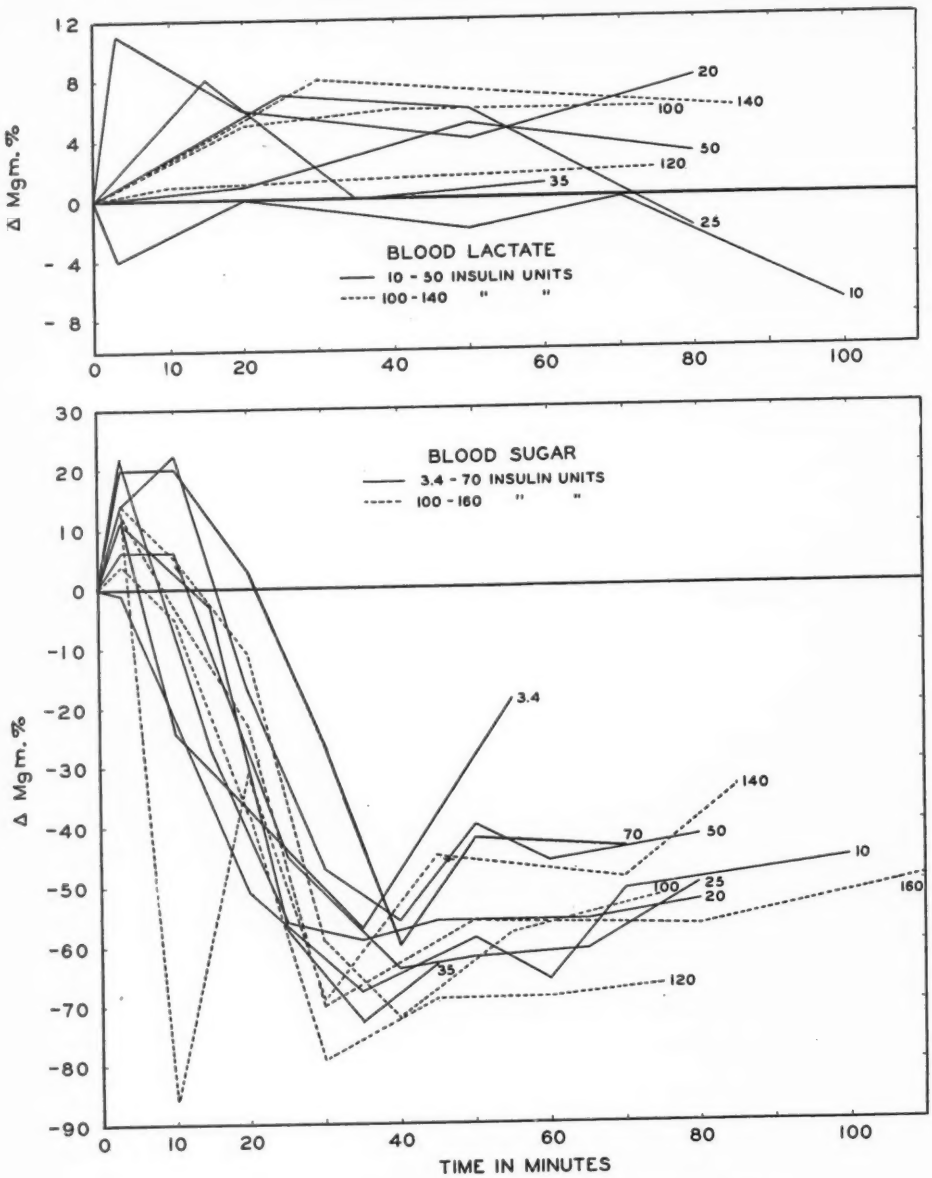

Fig. 2. CHANGES IN BLOOD SUGAR AND BLOOD LACTATE from basal levels in patient A.F. following intravenous insulin.

According to Dameshek et al. (9) the intravenous injection of from 8 to 80 U caused a definite increase in the blood lactic acid. However, in the present study insulin did not cause any appreciable change in blood lactate over the basal level except in resistant cases (fig. 2). This was in agreement with the report of Cori (14) working on animals.

The initial increase in blood sugar following intravenous injection was probably caused by some impurity in the insulin. Injection of insulin prepared from zinc crystals was not followed by this primary hyperglycemic response. Marble and Vartianinin (15) reported that insulin prepared from amorphous material or from zinc crystals causes a prompt fall of the

TABLE 4. BLOOD SUGAR CHANGES IN SCHIZOPHRENIC PATIENTS FOLLOWING SUBCUTANEOUS ADMINISTRATION OF MASSIVE DOSES OF INSULIN

Subject	Insulin, U	Basal	Time in minutes, after insulin 15	25	40	50	73	108	130	145	165	195	235
							Blood sugar values, mg. per cent						
A.F.	500	96		50	39		40	41	39		30	28	23
	500		86		67	23	38	36		24	29	21	26
C.H.	320	93		76	67		51	55	50		40	61	34
	320		74		58	50	31	32		22	20	21	
H.P.	320	100		82	84		60	47	41	56	44	46	
	320		86		58	58	47	44	44		31	21	31*
							Blood lactate values, mg. per cent						
A.F.	500	22.4			22.4		23.6	25.8			21.3		19.1
	500		29.2			33.7			22.4		33.5		29.2
C.H.	320							10.1					
	320		23.6				21.3	20.2				23.6	
H.P.	320	28.0					24.7					13.5	
	320		22.4			22.4					16.8		

*Intravenous glucose.

blood sugar of normal and diabetic individuals which is almost identical in rate when administered intramuscularly.

The fall in the blood sugar level was very rapid after the initial rise, usually reaching its lowest value approximately 30 to 40 minutes after the injection. The appearance of perspiration frequently occurred at this time, but there was no clear relationship between the blood sugar and the apparent depth of coma. Because of the fluctuations in the blood sugar concentrations it was impossible to be sure that we had succeeded in getting the lowest points. Recovery from the hypoglycemia was spontaneous but slow.

A most interesting aspect of this study is the apparent lack of correlation between the dose of insulin given and the level to which the blood sugar was lowered. Doses of 120 U produced no greater effects than did doses of 30 U. In one subject 160 U failed to lower the blood sugar to the same extent as 50 U had done previously. However, in most cases the lowest values were close to the expected concentrations of nonfermentable reducing substances. According to Forbes and Czarske (2) this concentration is about 20 mg.% and it is therefore possible that in many instances capillary blood may have been virtually glucose-free. While there may be an insulin dose that produces a maximal effect both on blood sugar and on the other evidences of hypoglycemia, such as coma or convulsions, our observations do not warrant a recommendation.

TABLE 5. DATA ON SUBJECTS

Subject		Ht.	Wt.	Age	Diagnosis	Previous Treatment
			lb.	yr.		
A.F.	♂	5′11″	150	23	D. P. Catatonic	C; M; I.I.
J.C.	♂	6′0″	163	31	D. P. Hebephrenic	None
H.P.	♂	5′8″	128	27	D. P. Hebephrenic	C; M; I.I.
A.G.	♂	5′1″	114	38	D. P. Hebephrenic	C; M; I.I.
J.R.	♂	5′10″	138	31	D. P. Hebephrenic	C; M; I.I.
B.G.	♂	5′6″	144	34	D. P. Paranoid	M
C.H.	♂	5′11″	140	22	D. P. Hebephrenic	C; M; I.I.
B.S.	♀		163		Chronic Manic	None
A.W.	♀		132		D. P.	None
O.M.	♀		108		D. P.	None
C.F.	♀		122		D. P.	None

C=camphor; M=metrazol; I.I.=intramuscular insulin

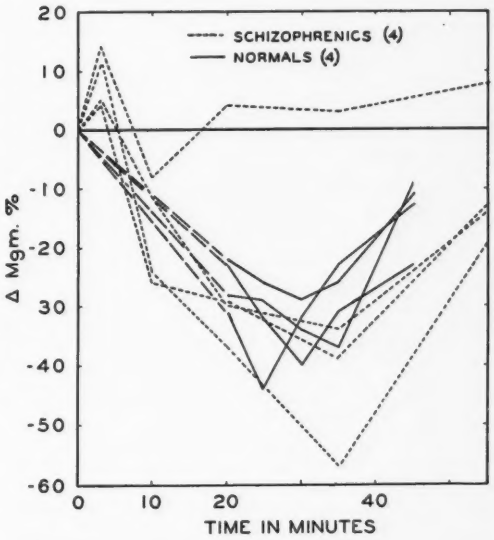

Fig. 3. CHANGES IN BLOOD SUGAR OF NORMAL AND SCHIZOPHRENIC SUBJECTS from basal levels following a test dose (0.05 U/kg.) of insulin intravenously.

Corwin (8) has stated that the resistance of dogs was decreased as the result of successive insulin injections. This decreased resistance became more or less stabilized after the third day. We cannot state that the resistance to insulin was altered one way or the other by frequent injections.

The reactions of schizophrenics, as regards insulin, appear to be somewhat abnormal. This is substantiated by comparing the responses of the patients to those of normal men. The schizophrenic patients showed a greater drop in blood sugar and a more retarded return to normal levels or, as in one case, practically no change whatsoever. Schizophrenic patients are able to tolerate massive doses of insulin, but the phenomenon has not been explained. There is the possibility that a deranged autonomic nervous system may in some manner be responsible for schizophrenia and expresses itself in this and other abnormal tolerances. But it should be noted that one of the female patients, who received 160 U intravenously, was not a schizophrenic but a chronic manic.

SUMMARY

Both male and female schizophrenic patients tolerated massive intravenous doses of insulin.

Blood lactic acid was not appreciably altered as the result of insulin injection.

The onset of sweating and the lowest level of blood sugar generally occurred approximately 30 minutes following the injection of insulin.

A larger dose of intravenous insulin did not necessarily result in a more pronounced effect. In many cases larger doses produced smaller effects.

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Relative Effectiveness of Several Methods of Administering Desoxycorticosterone Acetate[1]

[Addison's Disease]

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Successful hormone therapy depends in a large measure upon three factors, *a*) a satisfactory hormone preparation of uniform potency, *b*) moderate cost of adequate therapy and *c*) a convenient and effective method of administering the hormone. Desoxycorticosterone acetate, a synthetic adrenal cortical hormone, has been employed successfully in the treatment of patients with severe adrenal cortical insufficiency (1). The crystalline hormone preparation ensures uniform potency and it is possible to maintain an effective concentration of hormone by means of a single, daily intramuscular injection of the hormone in oil or by the subcutaneous implantation of pellets of crystalline hormone at intervals of 12 to 14 months. Furthermore, most patients can afford the cost of synthetic hormone therapy. Limiting factors in the exclusive use of desoxycorticosterone therapy are its deficiency in the 'carbohydrate-regulating factor' of the adrenal cortex and the care which must be exercised in the administration of this preparation in order to prevent the occurrence of overdosage phenomena (1).

Methods of administering desoxycorticosterone acetate, other than by intramuscular injection of hormone in oil or subcutaneous implantation of pellets have been attempted (2, 3). These methods have had as their aim the elimination of the necessity for daily injections of hormone in oil or for surgical implantation of pellets.

Experimentally it has been shown that the oral administration of desoxycorticosterone acetate is unsatisfactory (3) whereas some success has been attributed to the administration of the hormone by inunction (2). Recently, Anderson, Haymaker and Henderson (4) reported success in the treatment of patients with Addison's disease with desoxycorticosterone acetate administered sublingually. These authors claim that not only is the sublingual route of administration effective but also that apparently the efficiency of a propylene glycol solution of the hormone administered sublingually in divided doses, 5 to 6 times daily, is equivalent in effect to an equal quantity of hormone in oil, injected intramuscularly once daily.

The present study was undertaken to determine the relative effectiveness of administering desoxycorticosterone acetate sublingually, orally, by inunction and as a suppository, as compared to a single daily intramuscular injection of the hormone in oil or pellets of the crystalline hormone implanted subcutaneously. Four bilaterally adrenalectomized dogs were used for experimental studies, and the clinical observations were made on five patients with classical signs and symptoms of Addison's disease.

Both the experimental animals and the patients with Addison's disease were provided with a constant sodium chloride intake throughout the study.

METHODS

Experimental Animals. Bilaterally adrenalectomized, castrate, male dogs[3] (approximately 15–20 kg.) were maintained in metabolism cages and fed a constant diet composed of 400 gm. of ground beef to which was added 50 cc. of irradiated, evaporated milk. At the completion of each 24-hour period the animals were catheterized and weighed. Twenty-four-hour urine specimens were collected under toluene. Following a 15-hour fast specimens of blood were withdrawn under oil from the jugular vein, care being taken to avoid stasis. The methods used in the analysis of blood, urine and diet specimens have been described (5).

Received for publication October 6, 1941.

[1] This study was aided by a grant from the Committee on Research in Endocrinology, National Research Council.

[2] Scholarship from Institute of International Relations from University of Brazil, Rio de Janeiro.

[3] We are indebted to Doctor Warfield M. Firor of the Department of Surgery for preparing the adrenalectomized, castrate animals.

Desoxycorticosterone acetate in sesame oil,[4] 1 cc. of oil containing 5 mg. of hormone, was injected intramuscularly once daily. Sterile pellets of crystalline desoxycorticosterone acetate (125 mg. each) were implanted subcutaneously with local anesthesia (a solution of 1:200 procaine HCl). Desoxycorticosterone and desoxycorticosterone acetate in propylene glycol (1 cc. containing 6, 8 or 10 mg.) were administered by medicine dropper under the tongue and the dog's mouth was held tightly closed for approximately one minute. The hormone solution in propylene glycol was also given orally, the dose of hormone in propylene glycol having been mixed with approximately 10 gm. of meat, and the bolus of meat then being placed well back in the animal's throat to facilitate its being swallowed immediately. An inunction of desoxycorticosterone acetate in cocoa butter was prepared in which 10 mg. of hormone was contained in 1.5 gm. of the ointment. A site approximately 5 cm. in diameter on the back of the animal was shaved and kept free of hair. The dose of ointment was weighed out on wax paper and transferred to the prepared site with a spatula. The ointment was then rubbed into the skin using the forefinger covered with a finger cot. Five to 10 minutes was employed in rubbing in the ointment. The site was not cleaned between applications. Suppositories of desoxycorticosterone acetate were also prepared with cocoa butter. Each suppository weighed 1.5 gm. and contained 10 mg. of desoxycorticosterone acetate. The suppositories were inserted beyond the anal sphincter after the animal had defecated.

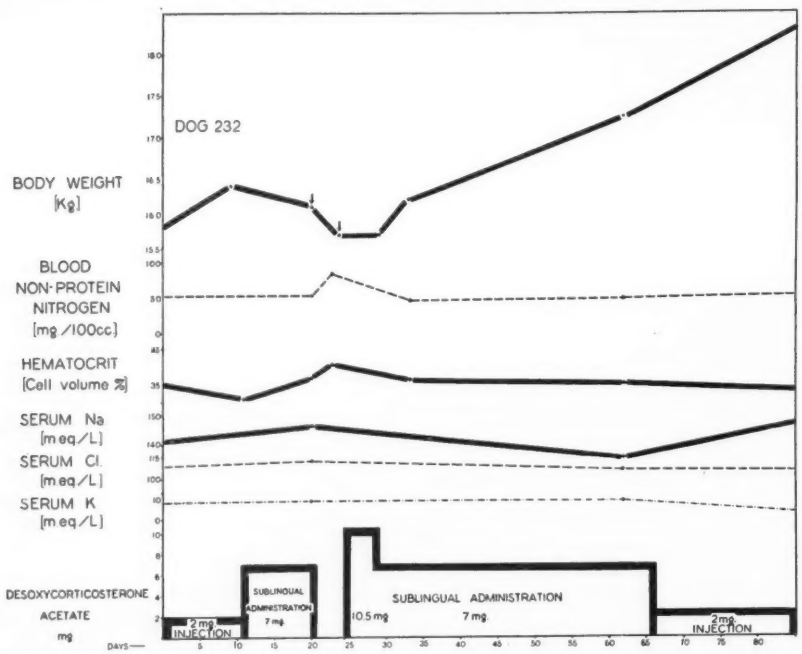

Fig. 1. Comparison of desoxycorticosterone acetate requirement of adrenalectomized dog 232 when administered by injection and sublingual routes.

Patients with Addison's Disease. All of the patients were studied on the metabolism ward of the Johns Hopkins Hospital. For the purpose of mineral balance studies each patient was provided with a constant diet and a constant fluid intake, the same items of food being ingested each day throughout the period of investigation. The patients were weighed each morning under fasting conditions. Twenty-four-hour urine specimens were collected under toluol. Specimens of blood for chemical analyses were withdrawn under oil and without stasis from the ante-cubital vein, the patients having fasted for 15 hours previously. The methods which were used in the chemical determinations of blood and urine specimens have been described (6).

The same hormone preparations were used in the clinical studies as were used in the studies on experi-

[4] We are indebted to Dr. E. Oppenheimer of the Ciba Pharmaceutical Products, Inc., Summit, N. J. for the desoxycorticosterone acetate in sesame oil (Percorten), the sterile pellets of desoxycorticosterone acetate, the solution of desoxycorticosterone acetate in propylene glycol and the crystalline desoxycorticosterone which was used in preparing the suppositories and inunction.

mental animals. The propylene glycol solution of desoxycorticosterone acetate was held under the tongue for 1 to 2 minutes before being swallowed. The solution was administered 5 to 6 times daily. The hormone was not given orally to patients with non-protein nitrogen level and the hematocrit (% volume of packed cells) are maintained within normal values. Withdrawal of therapy is followed within 2 to 5 days by loss of appetite, loss of weight, hemoconcentration, rise in blood N.P.N., lowering of serum

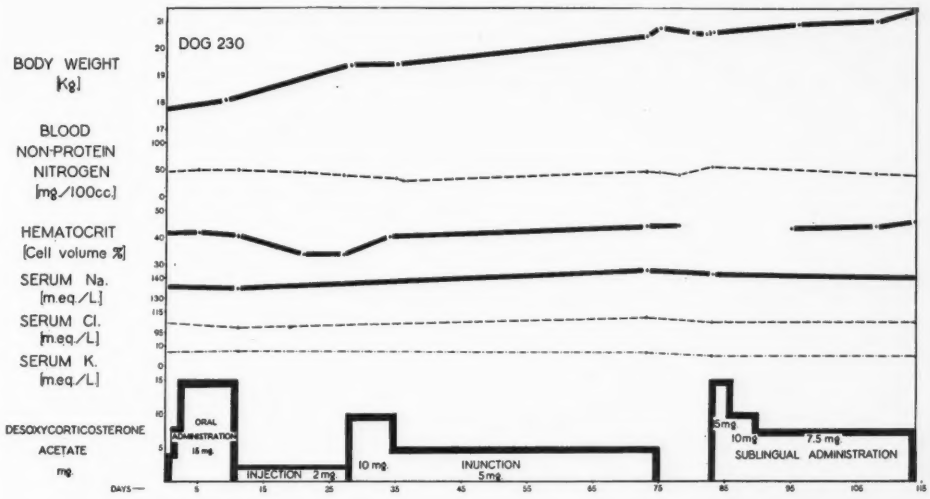

Fig. 2. Comparison of desoxycorticosterone acetate requirement of adrenalectomized dog 230 when administered by oral injection, inunction and sublingual administration.

Addison's disease because of previous experience with the poor results which attended this method of administration. Suppositories of hormone were inserted beyond the anal sphincter and were usually given night and morning. The inunction was rubbed in the axilla or on the inner aspect of the arms or legs for a period of 10 to 15 minutes. The inunction was applied 2 or 3 times daily.

OBSERVATIONS

Experimental Animals

Desoxycorticosterone acetate in sesame oil. Numerous and repeated studies which have been made during the past 3 years (5, 7) have indicated that bilaterally, adrenalectomized male dogs (10–20 kg.), maintained on a raw meat diet without added NaCl therapy, require not less than 1 mg. and not more than 2 mg. of desoxycorticosterone acetate in oil daily (fig. 1, 2, 3). In most of the animals 2 mg. of this hormone represents a dose somewhat in excess of the daily maintenance requirement after the animal has been restored to normal weight and a state of good health. On a maintenance dose which consists of 1 to 2 mg. of desoxycorticosterone acetate in oil injected once daily, the animals eat well, there is no excessive loss of sodium and chloride in the urine or excessive retention of potassium in the blood. On this regimen the serum concentration of electrolytes, the blood Na and Cl, and a rise in serum K, When treatment with the oil solution has been continued for some period there is frequently a delay of several days after hormone therapy has been discontinued before

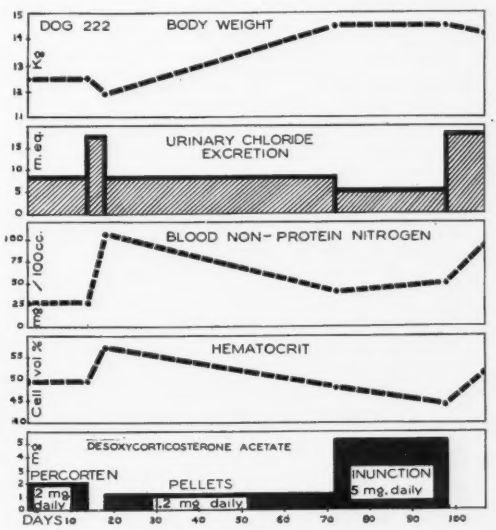

Fig. 3. Comparison of desoxycorticosterone acetate requirement of adrenalectomized dog 222 when administered by injection in oil, pellet and inunction.

marked symptoms of insufficiency develop. It is thought that this delayed appearance of symptoms may be due to the absorption of small deposits of hormone in oil which may have accumulated subcutaneously or intramuscularly. In the absence of infection or other complications, the fasting blood glucose level

TABLE 1. SUMMARY OF THE RELATIVE EFFECTIVENESS OF SEVERAL METHODS OF ADMINISTERING DESOXYCORTICOSTERONE ACETATE
(*Adrenalectomized Dogs*)

Mode of administration	Total daily maintenance dose of hormone	Frequency of administration
	mg.	
Pellets (3) 125 mg. each; implanted subcutaneously	1.2	once in 10 months
Injection: subcutaneous hormone in oil	2.0	once daily
Inunction	5.0	twice daily
Sublingual	6.0	two-three times daily
Oral	15.0	twice daily
Suppository (rectal)	15.0	twice daily

During these experiments the adrenalectomized dogs were maintained on a constant mineral intake of low sodium chloride content.

of adrenalectomized dogs maintained with desoxycorticosterone is within normal range. This is true despite the fact that it is well established that desoxycorticosterone acetate does not exhibit the 'carbohydrate-regulating effect' of adrenal cortical extract (1). It appears that in dogs (carnivora) there is a species variation in relationship to the dependence of blood glucose level on adrenal cortical hormone in the absence of infection or conditions of stress.

Pellets of crystalline desoxycorticosterone acetate. Pellets of crystalline hormone, which were prepared under carefully standardized conditions and which weighed approximately 125 mg. each, were implanted subcutaneously in the scapular region under local anesthesia. Standardized pellets of this size were absorbed at a rate of approximately 0.35 mg. per day, per pellet, when pellets were permitted to remain in situ for not less than 30 days and not more than 300 days. For most dogs, 3 pellets (approximately 1.2 mg. of hormone daily) sufficed for maintenance (fig. 3). Three pellets (weighing 125 mg. each) provided adequate therapy for approximately 10 months. The requirement of hormone, provided by pellet implantation, was approximately two-thirds of that required by a single, daily injection of desoxycorticosterone acetate (hormone in oil). Thus, the effect of 2 mg. of the oil preparation daily was paralleled by the effect obtained from 1.2 mg. of hormone, absorbed from pellets (table 1). All 4 of the adrenalectomized dogs are now being maintained in very good condition by means of 3 pellets of desoxycorticosterone acetate which were implanted subcutaneously. These data confirm earlier observations (8).

Sublingual administration of a propylene glycol solution of desoxycorticosterone acetate. In the experimental animals propylene glycol solution of hormone was administered in divided doses, 2 or 3 times daily. It was readily apparent that the maintenance dose of desoxycorticosterone acetate administered by intramuscular injection once daily was not sufficient for maintenance when given sublingually even in divided doses, since the animals rapidly lost weight. The weight loss was associated with hemoconcentration, a rise in blood N.P.N., increased excretion of Na and Cl, a reduction in the serum Na and Cl concentration and an increase in serum K concentration. When larger doses of hormone were administered sublingually, it was possible to maintain the animals in very good condition. It was also possible to restore them to good condition from an adrenal crisis by this method of therapy. Thus, it appeared that the sublingual administration of the hormone was an effective method of therapy. However, the quantity of hormone which was required by this route was considerably greater than that required by the injection of hormone in oil or from pellets. *Dog 232* (fig. 1) required at least 7 mg. daily of hormone, administered sublingually in divided doses in comparison to 2 mg. of desoxycorticosterone acetate in oil given as a single, daily injection. *Dog 230* (fig. 2) had approxi-

TABLE 2. COMPARISON BETWEEN THE EFFECTIVENESS OF SUBCUTANEOUSLY INJECTED AND SUBLINGUALLY ADMINISTERED DESOXYCORTICOSTERONE ACETATE
(*Addison's Disease*)

Patient	Maintenance dose of hormone in oil	Dose of sublingually administered hormone	Ratio of subcutaneous: sublingual dose	Remarks
	mg.	*mg.*		
P.W.	5	5	1:1	sublingual insufficient
E.V.	4	8	1:2	sublingual insufficient
H.U.	6	15	1:2.5	sublingual insufficient
L.V.	7.5	22.5	1:3	sublingual almost sufficient
H.S.	6	20	1:3.3	Sublingual equal to injection and sufficient for maintenance

Patients P.W., L.V. and *H.S.*, were maintained on diets of constant mineral composition throughout the period of these studies.

mately the same requirement, that is 7.5 mg. of hormone, sublingually as compared to 2 mg. of desoxycorticosterone acetate in oil. In one animal (*dog 223*) the sublingual administration of 4 mg. of hormone appeared to be adequate for maintenance. In this ani-

mal however, 2 mg. of the injected hormone in oil was somewhat greater than the necessary maintenance dose. Thus, in the 4 adrenalectomized dogs the average daily requirement of hormone administered sublingually approximated 6 mg. per day. The daily hormone requirement when administered sublingually as compared to the daily requirement of the hormone in oil, administered subcutaneously approximated a ratio of 3:1, the ratio of hormone requirement administered sublingually as compared to the pellet requirement approximated 5:1 (table 1).

Oral administration of a propylene glycol solution of desoxycorticosterone acetate. Dog 230 was treated for 11 days with a propylene glycol solution of desoxycorticosterone acetate administered in a bolus of food. It was observed that 15 mg. of hormone, administered by this method, in divided doses twice daily, maintained the dog in good condition and resulted in the establishment of a normal electrolyte balance (fig. 2). It appeared that the dose of hormone required by this method of therapy was 5 to 7 times that of the injected hormone in oil and 8 to 10 times that required by pellet therapy. More extensive experiments were not made with the propylene glycol solution administered orally since previous work in this laboratory (unpublished data) and the studies of others (3) have consistently shown that a relatively large dose of desoxycorticosterone acetate is required when the hormone is administered orally.

Desoxycorticosterone acetate administered by inunction. Dog 230 (fig. 2) and dog 222 (fig. 3) were treated with an inunction of desoxycorticosterone acetate for 47 and 26 days respectively. In both animals it appeared that 5 mg. of hormone administered in divided doses twice daily was adequate for maintenance. The transient increase in the excretion of Na and Cl which occurred during the first 2 or 3 days of inunction therapy indicated that the maximum effect from a given dose-level of hormone was not attained immediately. Furthermore, when inunction therapy was discontinued, there was a similar delay before the appearance of symptoms of adrenal insufficiency became manifest. The ratio of the hormone requirement by inunction to that by injection in oil approximated 2.5:1; the ratio of inunction to pellet requirement was 4:1.

From the studies on these 4 animals it appeared that hormone administered by inunction, although somewhat time-consuming (5–10 minutes, twice daily, per animal) was quite effective. The average daily maintenance dose required by inunction appeared to be slightly less than that required by sublingual administration.

Desoxycorticosterone acetate, administered by rectal suppository. This method of administering hormone, although somewhat impractical, was investigated in an effort to determine whether the requirement of hormone absorbed from the rectal mucosa differed essentially from that of the absorption of hormone from the sublingual area, and from the gastric and small intestinal mucosa (oral therapy). Studies were made on 2 dogs (222 and 223) and it was observed that a satisfactory condition could be maintained only when 10 to 20 mg. of hormone were given daily in divided doses. Extrusion of unabsorbed suppositories made the apparent hormone requirement somewhat greater than was actually the case. It appeared from these data, however, that the requirement of hormone by rectal suppository (15 mg. daily) was approximately of the same order of magnitude as the quantity of hormone in propylene glycol required by oral administration.

Patients with Addison's Disease

Desoxycorticosterone acetate in sesame oil. In clinical therapy it has been found possible (6, 9, 10) to maintain an effective concentration of desoxycorticosterone acetate throughout 24 hours by means of a single daily intramuscular injection of hormone in oil. The hormone requirement of individual patients varies greatly, from 0.5 to 15.0 mg. daily. However, in most instances patients require 5 mg. or less per day. The hormone requirement is of course modified significantly by the quantity of supplementary NaCl which is ingested as well as by the K content of the diet.

Pellets of crystalline desoxycorticosterone acetate. Pellets (125 mg. each) composed of crystalline hormone have been implanted subcutaneously in patients with Addison's disease following a period of treatment with daily injections of the hormone in oil (11). The number of pellets implanted in an individual case is determined by a preliminary assay with injections of desoxycorticosterone acetate in oil. Pellets which weigh approximately 125 mg. usually provide continuous and adequate therapy for a period of at least 12 months. The ratio of hormone requirement by injection to that of pellets of crystalline hormone implanted subcutaneously approximates 10:7 (11). This ratio in patients with Addison's disease corresponds very closely to that which has been observed in adrenalectomized dogs, 10:6 (vide supra).

Sublingual administration of a propylene glycol solution of desoxycorticosterone acetate. The relative effectiveness of administering desoxycorticosterone acetate sublingually was investigated in 5 patients with classical signs and symptoms of Addison's disease (*P.W.*, *E.V.*, *L.V.*, *H.S.*, and *H.U.*). An attempt was made in treating *patient P.W.* to substitute an equivalent amount of hormone administered sublingually for the maintenance dose of desoxycorticosterone in oil (5 mg. once daily). Five mg. of the propylene glycol

solution were given in divided doses 5 times daily. On this latter regimen the patient lost weight, whereas previously on a single daily injection of the hormone in oil, his weight had been slowly increasing (fig. 4). A striking increase in urine volume and in Na and Cl excretion occurred during the sublingual administration of 5 mg. of hormone. During the period of sublingual therapy the patient complained of nausea and headache and his clinical condition became progressively less satisfactory. From the Na and Cl balance studies it was apparent that 5 mg. of hormone, administered sublingually in divided doses 5 times daily, was not equivalent in effect to 5 mg. of hormone in oil injected intramuscularly once daily.

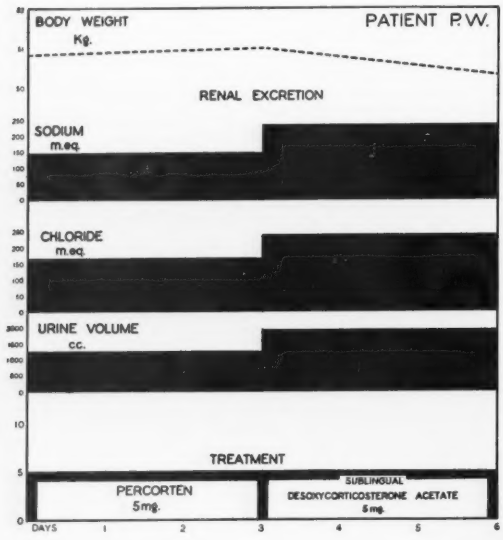

Fig. 4. *Patient* P. W. ADDISON'S DISEASE. Comparison of desoxycorticosterone acetate requirement by injection and sublingual routes of administration.

In treating *patient E. V.*, the daily dose of hormone administered sublingually was increased to twice the maintenance dose of desoxycorticosterone acetate in oil (4 mg. daily). Despite the increased quantity of hormone administered sublingually (8 mg. daily) this patient excreted 72.1 m.eq. of Na and 83.5 m.eq. of Cl daily during a 6-day period in contrast to a daily excretion of 64.3 m.eq. of Na and 74.4 m.eq. of Cl which were observed during a similar period of therapy with the hormone in oil (4 mg. daily). The patient, gained approximately 1.2 kg. during the latter period of therapy whereas no gain in weight occurred during the 6-day period of therapy by the sublingual route. Studies on this patient indicated that 4 mg. of desoxycorticosterone acetate in oil administered as a single daily intramuscular injection were more effective than 8 mg. of hormone administered sublingually in divided doses.

In treating *patient H. U.*, the quantity of sublingually administered hormone was increased to 2½ times the maintenance dose of hormone in oil (6 mg. daily). During a 48-hour period of therapy by the sublingual route (15 mg. daily in divided doses) it was observed that the renal excretion of Na and Cl increased approximately 25% above the excretion of these electrolytes during the preceding 6-day control period of therapy with the hormone in oil (6 mg. daily). The patient lost approximately 1 kg. in body weight during the 48-hour period of sublingual therapy (15 mg. daily) whereas body weight had been maintained throughout the preliminary period of therapy with desoxycorticosterone acetate in oil (6 mg. daily).

In *patient L. V.*, 22.5 mg. of hormone, administered sublingually in divided doses, was substituted for a daily maintenance dose of 7.5 mg. of injected hormone (fig. 5). On this regimen the patient maintained body weight and blood pressure (during the period in which she had been receiving 7.5 mg. of the hormone in oil daily there had been a slight daily increase in body weight). The renal excretion of Na and Cl (fig. 5) was increased somewhat during the period of sublingual therapy. The hematocrit remained unchanged. On the day that the injection

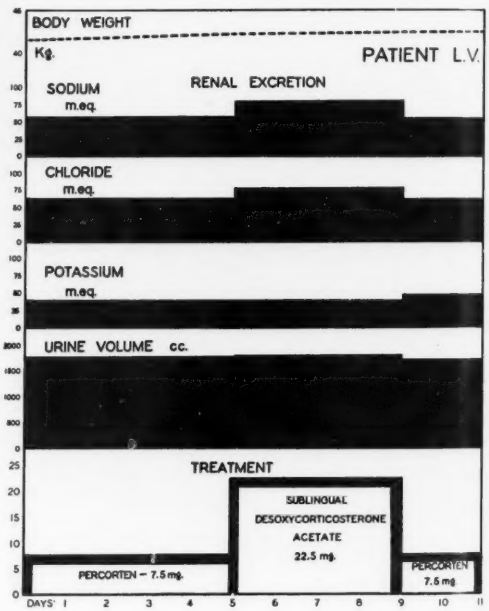

Fig. 5. *Patient L. V.* ADDISON'S DISEASE. Comparison of desoxycorticosterone acetate requirement by injection and sublingual administration.

type of therapy was again substituted, a slight increase in the renal excretion of K was noted. These changes suggest that a single, daily injection of 7.5 mg. of desoxycorticosterone acetate in oil was slightly more effective than 22.5 mg. of the hormone administered sublingually in divided doses.

Sublingually administered hormone (20 mg. daily in divided doses) was substituted in *patient H.S.* (fig. 6) for 6 mg. of the hormone in oil injected once daily. On this regimen the patient's weight, blood pressure and electrolyte balance was well maintained. The Na and Cl excretion during the period of injection therapy amounted to 90.2 and 98.7 m.eq. respectively. The values during sublingual therapy were 90.9 and 95.9 m.eq. respectively. The studies in this patient indicated that an effect, equivalent to that of injection therapy, could be obtained with sublingually administered hormone when a sufficiently large dose was employed, that is, a ratio in excess of 3/1. It is of some interest to note that this ratio is of approximately the same order of magnitude as that observed in the studies on adrenalectomized dogs (table 1).

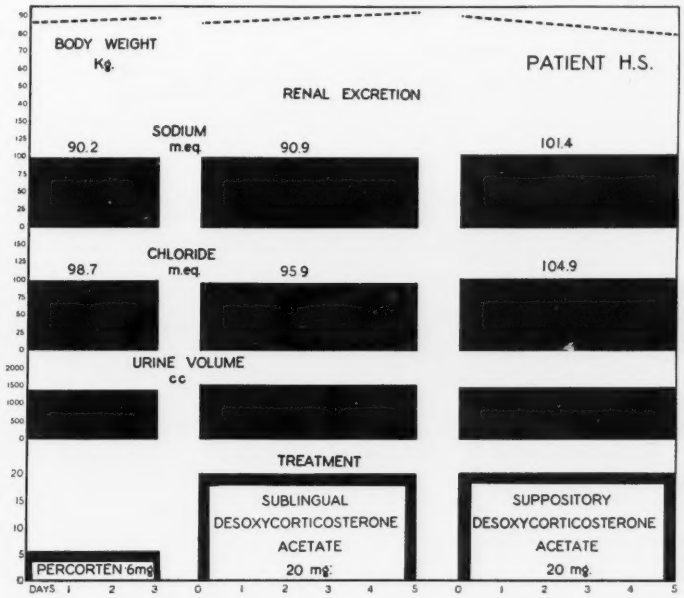

Fig. 6. *Patient H. S.* ADDISON'S DISEASE. Comparison of desoxycorticosterone acetate requirement by injection, sublingual and suppository modes of administration.

Desoxycorticosterone acetate administered by inunction. The effectiveness of treatment with hormone in cocoa butter applied as an inunction was studied in 2 patients on the Metabolism Ward (*H.U.*, and *L.V.*) and in one patient (*D.B.*) in the Dispensary. *Patient H.U.*, required 6 mg. of desoxycorticosterone acetate in oil daily for satisfactory maintenance. When 30 mg. daily of the hormone, applied in divided doses as an inunction, was substituted the patient lost weight (0.4 kg. in 72 hours) and her blood pressure decreased from a level of 130/84 to a level of 108/74 mm. Hg. Because of the onset of anorexia and malaise the injection mode of therapy (6 mg. daily) was resumed. The patient gained 0.8 kg. during the ensuing 48 hours of injection therapy and her blood pressure increased to a level of 120/76 mm. Hg.

Patient L.V., had been steadily gaining weight during a period in which she was receiving 3 mg. daily of the hormone in oil by injection. During a 3-day period in which she was given a total of 70 mg. of hormone by inunction (average of 23.3 mg. daily) she lost 0.9 kg. No alteration in blood pressure was observed. Desoxycorticosterone acetate in oil therapy (3 mg. daily) was then resumed and the patient gained 0.4 kg. during the ensuing 72 hours.

The studies in these 2 patients indicated that relatively large doses of hormone (5–7 times the maintenance dose of hormone injected in oil) in cocoa butter applied as an inunction were not sufficient for maintenance.

Because studies on adrenalectomized dogs had indicated that a delay of 48 to 72 hours might occur before the maximum effect from any given dose level of hormone applied by inunction had been attained, a patient with less severe symptoms was treated as an outpatient for a period of 10 days with 15 mg. (7.5 mg. twice daily). Prior to this study this patient

had been receiving a constant quantity (5 gm.) of added NaCl without added hormone. With no other change in his regimen the daily inunctions of hormone were instituted. It was of considerable interest to note that this patient failed to gain weight during a 10-day period in which the inunction was applied. Furthermore, there was no evidence of hemodilution or increase in blood pressure during this period. These latter changes are observed almost invariably when appreciable quantities of the hormone are absorbed from intramuscular injections or from pellets. Although this type of experiment is not conclusive, it does support the observations which were made in the two other patients, namely that hormone in cocoa butter applied as an inunction did not appear to be a very efficient method of treatment in patients with Addison's disease.

Desoxycorticosterone acetate, administered as a suppository (rectal). The administration of hormone in rectal suppositories of cocoa butter was studied in *patient H.S.*, (fig. 6). During a preliminary period in which 6 mg. of the hormone in oil was administered by injection, this patient slowly gained weight and the renal excretion of Na and Cl amounted to 90.2 m.eq., and 98.7 m.eq., respectively. Treatment with suppositories of hormone was then substituted. During the first 2 days of treatment a single suppository containing 10 mg. of hormone was given following the administration of a plain water enema. On the 3rd and 4th days the dose was increased to 20 mg. daily (10 mg. suppository being given in the morning and evening) and on the 5th day the total dose was increased to 30 mg. Despite these rather large doses of hormone the patient lost 0.8 kg. during this period and the 24-hour renal excretion of Na and Cl increased to 101.4 m.eq. and 104.9 m.eq. respectively (fig. 6). During this period the patient also failed to maintain the level of clinical improvement which had been attained during the period of injection therapy. From this experiment it appeared that 10 to 30 mg. of hormone (18 mg. average daily dose) administered by rectal suppository was less effective than 6 mg. of hormone injected intramuscularly once daily.

DISCUSSION

A careful distinction should be made between the efficacy of a hormone preparation and the relative efficiency of a particular mode of hormone administration. It seems apparent from these studies and from those of other investigators that desoxycorticosterone acetate, once it has access to the blood stream in suitable concentration represents an efficacious form of therapy for the majority of patients with Addison's disease. The proof of this requires months of continued observation in a large series of patients and the possible effect of diet, NaCl and K intake must be given careful consideration. The relative efficiency of any method of administering desoxycorticosterone, however, may easily be determined within a few days by an appropriate study of the renal excretion of Na Cl and K since the regulation of the renal excretion of these electrolytes appears to be one of the principal functions of the hormone. Such a brief period of study of course, may give little or no information regarding the adequacy of the particular dose of hormone with respect to life maintenance. In studying the efficacy of desoxycorticosterone in the treatment of Addison's disease, it is necessary to exclude additional NaCl medication if a critical analysis of the therapeutic benefits is to be made, whereas in a study of the relative efficiency of various methods of administering desoxycorticosterone acetate it is only necessary to ascertain that the NaCl intake is constant throughout comparative periods.

From long-continued studies on adrenalectomized dogs it is evident that the sublingual administration of a propylene glycol solution of desoxycorticosterone acetate is an efficacious form of therapy provided that an adequate quantity of hormone is administered. The clinical studies are of too short duration to substantiate this point. However, there is no reason to doubt the observations of Haymaker and Anderson in this regard since the present studies indicate that the administration of sufficient hormone sublingually will maintain electrolyte balance in patients with Addison's disease.

From the studies in both the experimental animals and in patients it is obvious however, that the sublingual administration of hormone is by no means as efficient as the intramuscular administration of hormone in oil or the subcutaneous implantation of pellets. On this point the results of the present investigation are in disagreement with the parity which Haymaker and Anderson describe for sublingual and subcutaneously injected hormone. Until further evidence is obtained it is recommended that if sublingually administered hormone is substituted for daily injections of hormone, the initial dose of sublingually administered hormone should be *at least* 3 times the maintenance dose of injected hormone. It is probable that the greatly increased cost of sublingual therapy will restrict its clinical application in the treatment of patients with a relatively high hormone requirement. Thus far no toxic symptoms have been observed in either experimental animals or patients from the propylene glycol solution.

It is quite possible that substances other than cocoa butter may be more suitable for inunction in human subjects. Because of the relatively good results which were obtained in dogs with the use of inunction, further clinical studies on this method of therapy would appear to be indicated. The oral or rectal administration of the available preparation of desoxycorticosterone acetate does not appear to be feasible.

SUMMARY AND CONCLUSIONS

Bilaterally adrenalectomized dogs were maintained in good condition on a diet of low NaCl content when treated with preparations of desoxycorticosterone acetate as follows.

Subcutaneous implantation of pellets	1.2 mg. daily
Subcutaneous injection of hormone in oil	2.0 mg. daily
Percutaneous administration (hormone in cocoa butter)	5.0 mg. daily
Sublingual administration (propylene glycol solution)	6.0 mg. daily
Oral administration (propylene glycol)	15.0 mg. daily
Rectal administration (cocoa butter suppository)	15.0 mg. daily

For patients with severe Addison's disease at least three methods of administering desoxycorticosterone acetate appear to be feasible at present, *a*) implantation of pellets, *b*) intramuscular injection of hormone in oil and *c*) sublingual administration of a propylene glycol solution of hormone. The ratio (approximate) of the desoxycorticosterone acetate requirements when administered by these three methods is as follows:

1 mg. (pellets) : 1.3 mg. (in oil) : 5 mg. (sublingual).

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PROTOCOLS

H. S. (*No. 217776*) a white, married, business man, 48 years of age, was admitted to The Johns Hopkins Hospital on Dec. 26, 1940 complaining of weakness. In 1922 he had been discovered to have spondylitis and he was subsequently treated at the Rollier Clinic, Switzerland, from which he was discharged as being completely cured. He remained well and active until the spring of 1936 when he noticed weakness and fatiguability in association with increased pigmentation of his skin. Nocturia developed and he consulted a urologist. A moderate degree of prostatic infection was noted and in addition it was suggested that the patient was suffering from Addison's disease. Irradiation therapy to the prostate was administered, following which the patient had a severe episode of vomiting and weakness. He states that his systolic blood pressure fell below 90 mm. Hg. Treatment with adrenal cortical extract was instituted and continued from 1936 to 1939. From April 1939 until his admission to The Johns Hopkins Hospital (Dec. 1940) this patient had received only NaCl therapy.

Physical examination revealed a well developed man rather deeply pigmented who did not appear to be acutely ill. His blood pressure was 110/80 mm. Hg, pulse rate 84, temperature 98.2° F. and body weight 80.0 kg. (176 lbs). His skin was diffusely tan, being darkest over the neck, in the anterior folds of the axillae and in the creases in the palms of the hands. The lips and lower gums were deeply pigmented with bluish-black areas. The thyroid was not enlarged. The cardiac measurements were within normal limits. The heart sounds were somewhat distant. The second pulmonic sound was accentuated. The prostate was small and hard with two hard, pea-sized nodules at the base. The left epididymis was indurated and moderately enlarged. Otherwise the physical examination was not remarkable.

Blood studies revealed the hematocrit to be 47% cell volume, the W.B.C. 11,000 with polymorphonuclears 56% and lymphocytes 44%; blood N.P.N. 34 mg., blood sugar 99 mg., and serum protein 6.1 gm. per 100 cc., serum Na 141.8, serum Cl 104.0, serum CO_2 combining power 27.5 and serum K 4.3 m.eq. per liter.

The specific gravity of the urine was 1.010. No sugar or albumin was noted. Ten W.B.C. per highpower field were noted; a positive culture for tubercle bacilli was obtained. Tuberculin test was positive in a dilution of 1:100,000. Phenolsulphonphthalein excretion was 68% in 2 hours with 45% in the first 30 minutes. Roentgenograms of the chest and sella turcica revealed no abnormalities. A calcified area which was located above and to the left of the pineal body was evident. No calcification in the region of the adrenals was observed. An old destructive lesion involving T9 and T10 was noted in the spine. Electrocardiograms revealed a normal sinus rhythm and a levogram without definite evidence of myocardial damage.

Patient L. V. (*No. 220074*) a white, married female, 43 years of age, was admitted to The Johns Hopkins Hospital on Jan. 15, 1941 complaining of weakness, nervousness and increasing pigmentation. In 1938 she first noticed that she was becoming increasingly nervous and irritable. During this year she had had amenorrhea for a period of several months. In 1939 the appearance of dark pigmentation over her cheeks and over the exposed portions of her arms and legs was noted. The pigmentation was most pronounced at pressure points such as the knees and elbows. She noticed no other unusual signs or symptoms at this time. In June 1940 the patient began to feel weak and tired. Her appetite decreased and she lost weight. At this time her condition was much worse and she appeared to be suffering from a rather severe adrenal crisis. Infusions of saline and glucose were given in addition to relatively large doses of Eschatin. She was discharged and treatment

with Eschatin (5 cc. daily) was recommended. The patient returned home improved but was still confined to bed for the greater part of the time. During her illness she had lost approximately 9 kg. in weight and she had noticed a decrease in the quantity of pubic hair. She had had no menstrual periods during the 6 months prior to admission to The Johns Hopkins Hospital. She had had 4 pregnancies and all her children are alive and well. There had been no history of tuberculosis either in the patient or her family.

Physical examination revealed a thin, emaciated woman who was too weak to sit up in bed for more than a few minutes at a time. Her blood pressure was 110/60 mm. Hg., pulse rate 110, temperature 99° F., and body weight 42.5 kg (93.5 lbs.). There was generalized dark brown pigmentation which was most marked over the knees, elbows, buttocks and palms of the hands. A scar in the right axilla was also deeply pigmented. There were numerous black freckles over the arms and neck. On the lips, buccal mucosa and hard palate were numerous areas of bluish-black discoloration. There was an area of vitiligo on the chin; the finger tips were also completely depigmented. The axillary hair was absent and the pubic hair was scanty. The retinal arteries appeared somewhat tortuous and the retinal veins were moderately dilated. The thyroid was small; the breasts were atrophic. There was marked limitation of extension at the shoulders and motion in the spine was somewhat limited. Otherwise the physical examination revealed no unusual findings.

Examination of the blood revealed the hemoglobin to be 10.4 gm.; R.B.C. 3.56 millions and W.B.C. 5,800 with polymorphonuclears 74% and lymphocytes 26%. Blood chemical examination revealed a N.P.N. of 26 mg., sugar 81 mg., and protein 5.5 gm., per 100 cc., serum Na 135.0 m.eq., serum Cl 103.0 m.eq., serum Co_2 combining power 25.8 m.eq., and serum K 4.6 m.eq., per liter. The blood Wassermann reaction was negative and the tuberculin test was negative (1 mg.). Urine examination revealed numerous white blood cells. Cultures of catheterized specimens were sterile. Basal metabolic rate was 1% below standard. Phenolsulphonphthalein test revealed 70% excretion in 2 hours with 25% in the first 30 minutes. Roentgenograms revealed no abnormalities in the chest, sella turcica or adrenal region. The electrocardiogram indicated a sinus tachycardia with a normal axis. T2 and T3 were inverted. T4 F was upright but of low amplitude. These changes suggested myocardial disease.

H. U. (*No. 220231*) a white, married female, 34 years of age, was admitted to The Johns Hopkins Hospital on Jan. 25, 1941 complaining of marked weakness, anorexia, loss of weight and increasing pigmentation. In June 1939, following the delivery of her 4th child she had failed to regain her strength. During the ensuing months she became progressively weaker. In December 1939 she first became aware of the increasing darkness of her skin. This was associated with the appearance of purplish colored patches over the gums and buccal mucous membranes. At this time she also noted that her gums bled frequently and rather profusely. Between January and April in 1940 her appetite became much poorer and she lost a considerable amount of weight (approximately 10 kg.). In April 1940 she was confined to bed. In June 1940 she was admitted to a local hospital because of nausea and vomiting. At this time a diagnosis of Addison's disease was made and the patient was subsequently treated with intravenous infusions of saline and glucose solutions supplemented by subcutaneous injections of adrenal cortical extract and later intramuscular injections of desoxycorticosterone acetate.

The patient stated that she had never been very strong. There was no history of tuberculosis. She had suffered from repeated infections and on one occasion had had a severe infection of the gums, 'trench mouth.'

On admission to The Johns Hopkins Hospital the patient appeared emaciated, weak and chronically ill. Her blood pressure was 100/50 mm. Hg., pulse rate 120, temperature 98.2° F. and weight 37.7 kg. (83 lbs). There was generalized tanning of the skin which was most marked beneath the eyes, in the folds of the neck, over the abdomen, over the sacrum and lumbar vertebrae and in the gluteal region. On the lips, buccal mucosa and hard palate there were numerous bluish-black areas of pigmentation. There were also numerous, small black freckles over the face and upper extremities. The gums were red and spongy in appearance. The thyroid was not enlarged. The breasts were rather small. The cardiac measurements were within normal limits. The heart sounds were forceful. The second pulmonic sound was definitely accentuated, and a loud systolic murmur was audible over the entire precordium, the point of maximum intensity being over the apex. The pulses were small and equal and the peripheral arterial walls seemed soft. The vaginal mucosa appeared red and extremely sensitive. Rectal examination revealed large, tender hemorrhoids. The physical examination otherwise was not remarkable.

Laboratory examinations revealed that the hemoglobin was 13.5 gm., R.B.C. 4.38 millions, W.B.C. 7,400 with 58% polymorphonuclears, 37% lymphocytes and 5% mononuclears. The blood Wassermann reaction was negative. The Mantoux test was positive in a dilution of 1:10,000. Blood chemical studies revealed a fasting blood glucose level of 85 mg., N.P.N. of 24 mg. and total serum protein of 6.1 gm. per 100 cc. The serum Na was 136.8 m.eq., serum Cl 104.2 m.eq., serum CO_2 combining power 22.5 m.eq., and serum K 6.7 m.eq. per liter. Examination of the urine revealed a specific gravity of 1.018 and the presence of albumin 2+. The sediment was loaded with W.B.C., R.B.C., and casts. Cultures were negative. Roentgenograms of the chest indicated a prominent pulmonic conus in the cardiac outline, engorgement of the pulmonary vessels and non-tuberculous infiltration of the lungs. There was no calcification in the region of the adrenals and no abnormality in the sella turcica. Electrocardiogram revealed a normal sinus rhythm and normal axis. T1 and T2 were slightly inverted; T3 was isoelectric.

Protocols of *patients P.W., E.V.*, and *D.B.*, have been published elsewhere (6, 12).

Abnormal Suprarenal Discharges in Angina Pectoris and Their Control by X-ray Therapy

[Adrenalin and Angina Pectoris]

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IN A PREVIOUS PAPER[1] the theory was advanced that angina pectoris accompanying effort is brought about by the anoxiating metabolic effect of sudden discharges of adrenalin upon the heart muscle whose sclerotic arteries are incapable of dilating sufficiently to compensate for the acute loss of oxygen caused by adrenalin in the myocardial tissue. The therapeutic effect of roentgen irradiation of the suprarenal glands in 100 cases of typical angina pectoris was reported in detail.

Indirect evidence could be pointed out in favor of this theory, such as the artificial provocation of typical anginal symptoms through injection of adrenalin, the common occurrence of anginal attacks in persons with tumors of the suprarenal medulla, and the analogy between the occurrence of physiological adrenalin discharges and of anginal attacks accompanying effort, emotion and cold. However, direct objective evidence in regard to the behavior of suprarenal secretory activity in angina patients both before and after treatment of the adrenal glands with roentgen rays was still lacking. In order to obtain more conclusive information about this basic question in the problem of the pathogenesis of angina pectoris, the following investigations were carried out with the use of a colorimetric method (2). This method measures adreno-cortical ('AC') compounds which circulate in the blood and which contain both adrenalin and, combined with it, suprarenal cortical sterols.

Fifty-one normal persons and 17 patients with angina pectoris were studied. The blood AC level was determined on empty stomach at rest, 2 to 5, and 15 minutes after exercise (climbing stairs, sitting up and reclining in bed). Seven of the angina patients who had been subjected to roentgen treatment of the suprarenal glands were reexamined after various intervals in the same manner. All determinations were carried out in duplicates.

Received for publication August 15, 1941.

[1] This study was aided by a grant from the Rockefeller Foundation.

Blood AC in Normal Persons

The blood AC level was determined by comparison with a standard solution containing 100 $\mu\mu$g. (billionths of a gram) per cc. of pure adrenalin, and the results are expressed in 'color units' compared with the 100 color units per cc. of the standard solution.

In 51 normal persons the blood AC at rest was found to vary between 60 and 222 color units per cc., with an average value of 156. In 14 of these persons exercise tests were performed (table 1). Half of them showed a slight fall of the total AC level after exercise, in the others it rose slightly or moderately (+11 to +37 color units per cc.) and in only one case was there a marked rise of +82 color units per cc., 2 minutes after exercise with subsequent return toward the original level. Figure 1 shows the normal average curve.

TABLE 1. EFFECT OF EXERCISE TESTS IN NORMAL INDIVIDUALS (males) ON THE BLOOD AC

Case	Age, yr.	Exercise. No. of steps	Blood AC (color units per cc.)			
			Before exercise	2–5 min. after exercise	15 min. after exercise	Maximal deviation
1	24	42	84	71	92	−13
2	44	68	133[1]	154[1]	143[1]	+25[1]
3	49	42	127	209	149	+82
4	23	42	136	159	141	+23
5	26	42	131	165	118	+34
6	60	42	141	135	125	−16
7	23	42	158	179	129	−29
8	24	42	160	162	139	−21
9	23	42	160	170	180	+20
10	23	42	162	173	167	+11
11	26	42	180	173	159	−21
12	24	42	190	227	186	+37
13	27	42	196	183	169	−27
14	31	42	200	186	190	−14
Average	30		150	165	148	+10

[1] Average of 4 experiments.

In 4 cases the qualitative changes of the AC compounds of the blood were examined more in detail by means of the so-called 'specificity ratio' (2, 3). In all instances the results indicated an increased amount of adrenalin present in the AC compounds 2 minutes after exercise, with return of the adrenalin portion toward normal within 15 minutes. This was the case also when the total amount of AC decreased after exercise instead of rising and is in agreement with the findings of Cannon (4) and Meythaler and Wossidlo

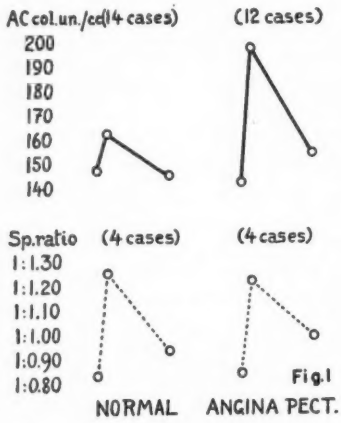

Fig. 1. AC color units in normal individuals and those with angina pectoris (solid lines). Specific ratios indicating temporary relative increase of adrenalin in total AC compounds after exercise (broken lines).

(5) concerning the stimulation of adrenalin secretion by physical exercise (table 2 and the dotted average curve in fig. 1).

Blood AC in Untreated Angina Pectoris Patients

The blood AC level at rest was found to be within normal limits (77 to 200, average 133, color units per cc.) in 12 of 13 compensated patients with typical angina pectoris. These 13 patients are included in table 3. In one of them (*case 21*) the blood AC was moderately elevated beyond normal (257 color units per cc.).

Furthermore, 4 decompensated patients with angina pectoris were examined. These do not appear in table 3 because no exercise tests were carried out in them. While the blood AC was normal (102, 169, 112 color units per cc.) in the 3 moderately decompensated cases, it was found elevated (276 color units per cc.) in the one with severe decompensation and pulmonary edema. A similar behavior of the blood AC has been observed in other patients with severe decompensation and pulmonary edema but without angina pectoris (6) and cannot be ascribed to the latter.

Table 2. 'Specificity ratio' in exercise tests on normal individuals

Case	Specificity Ratio[1]			
	Before exercise, 1:	After exercise		Maximal increase
		2–5 min. 1:	15 min. 1:	
4	1.06	1.72	1.41	0.66
11	0.82	1.22	0.85	0.40
12	0.73	1.13	0.74	0.40
2	0.82	1.05	0.82	0.23
Average	0.86	1.28	0.96	0.42

[1] 'Specificity ratio' means the ratio between the colorimetric results for AC compounds obtained with acid and alkaline treatment of the specimens (3, 10). An increase of this ratio in the direction toward 1:3.5 (specific ratio for pure adrenalin) indicates the presence of an increased amount of adrenalin within the AC compounds determined.

Neither does there exist any relationship between the blood AC level and the height of blood pressure. This is evident both from the cases mentioned in this paper and from a partly overlapping series of 36 cases of compensated essential hypertension (6) in which practically all AC findings ranged within normal limits.

In one patient who had been totally thyroidectomized 6 years ago without much improvement of his severe anginal attacks, and whose B. M. R. was −19%, the blood AC at rest was 77 color units per cc., thus near the lowest limit of normal and the lowest of all angina pectoris cases.

While the blood AC level in patients with angina pectoris did not show any regular abnormalities at rest, a significant and characteristic behavior was found after physical exercise (table 3) in that all 13

Table 3. Effect of exercise tests in untreated angina pectoris patients on blood AC

Case No. and sex	Age, yr.	Exercise No. of steps	Blood AC (color units/cc.)			
			Before exercise	After exercise		Maximal deviation
				2–5 min.	15 min.	
15, M	63	42	200	305	190	+105
16, F	46	42	113	191	140	+78
17, M	69	42	100	169	149	+69
18, M	67	8[2]	152	215	150	+63
19, M	67	42	140	202	145	+62
20, M	59	42	131	189	116	+58
21, F	49	42	257	310	233	+53
22, M	58	42	83	135	98	+52
23, M	58	30[2]	145	195	165	+50
24, F	73	10[2]	138	171	140	+33
25, F	65	42	131	162	152	+31
26, F	54	42	176	160	206	+30
31, M[1]	55	37	77	138	90	+61
Average	63		140	195	152	+57

[1] Thyroidectomized.
[2] Number of times sitting up.

patients examined (including the thyroidectomized one) showed a sharp rise of the blood AC, 12 with the maximum reached after 2 to 5 minutes, one after 15 minutes. All of these increases were higher than the normal average reaction. The qualitative 'specificity ratios,' which were determined in 4 cases, suggested a prevailingly strong increase of the adrenalin fraction of the blood AC, 2 to 3 minutes after exercise (table 4 and dotted average curve in fig. 1).

In summarizing it can be stated that in 13 patients with angina pectoris the blood AC level at rest was found to be normal but physical exercise was accompanied by an intense discharge of suprarenal adrenocortical hormonal compounds into the blood, usually of an abnormal degree and rich in adrenalin.

Blood AC in Angina Pectoris Patients after Roentgen Treatment of the Suprarenal Glands

Ten patients of the above discussed group were subjected to roentgen irradiation of the suprarenal glands by Dr. A. B. Soule with the same technic as described previously (1). The AC curve after physical exercise was re-examined after 1 to 8 months in 7 patients who had shown subjective improvement. No other treatments were given except in *case 18* (aminophyllin during a short relapse).

Figures 2 to 8 show graphically the behavior of the AC exercise reaction (upper curves) and the intensity of anginal complaints (black areas) before and after one series of roentgen treatment (small white squares) in 7 successfully irradiated patients.

These examples demonstrate the efficacy of roentgen irradiation of the suprarenal glands in regard to diminution or abolition of the AC discharges into the blood after physical exercise. When marked improvement or disappearance of the subjective symptoms after roentgen treatment occurred, it was accompanied by a corresponding disappearance of the characteristic intense AC discharges due to exercise. Delayed improvement, as in *case 23* (fig. 3, b), or complete relapse, as in *case 18* (fig. 6, c), was paralleled by the original intensiy of AC discharge after exercise.

TABLE 4. 'SPECIFICITY RATIO' IN EXERCISE TESTS ON UNTREATED PATIENTS WITH ANGINA PECTORIS

Case	Specificity Ratio			
	Before exercise 1:	After exercise		Maximal increase
		2–5 min. 1:	15 min. 1:	
24	0.70	0.94	0.74	0.24
26	0.93	1.20	1.03	0.27
22	0.83	1.14	1.02	0.31
25	1.00	1.70	1.30	0.70
Average	0.87	1.25	1.02	0.38

In *case 21* (fig. 2, b) the AC reaction was still present, although in a weakened degree, in a stage of only partial subjective improvement. Subsequently both the subjective symptoms and the AC reaction to

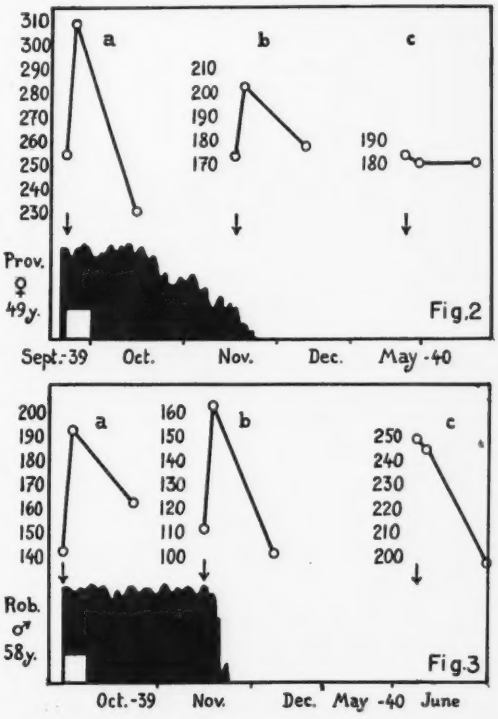

Fig. 2. *case 21*. Fig. 3. *case 23*. Solid lines represent reactions of blood levels of AC compounds to exercise tests (determined in each instance before, 2–5 and 15 minutes after exercise. Solid black area represents comparative intensity of anginal complaints, as described by patient. White square indicates series of X-ray treatment of the suprarenals.

exercise disappeared completely. In 4 instances the original sharp elevation of blood AC after exercise was reversed after roentgen treatment into a fall below the initial level.

The AC level at rest after roentgen irradiation of the suprarenal glands varied, being decreased in some, increased in others (table 5) but it remained always within normal range. One exception was *case 23* in which the AC level was found slightly above normal 8 months after treatment.

There was neither a characteristic influence upon the blood pressure level and its reactions to exercise (table 5), nor upon the pulse rate and its reactions.

DISCUSSION

Quantitative chemical determination of AC compounds (adrenalin plus cortical sterols) in the blood of patients with angina pectoris showed a normal resting

level but an abnormally intense elevation of the blood AC level for a few minutes after physical exercise. The proportion of adrenalin proper within the bulk of the AC compounds reached its maximum 2 to 3 minutes following exercise and subsequently returned toward normal within 15 minutes.

Parenterally administered adrenalin characteristically produces typical anginal symptoms (1, 7, 8, 9). Desoxycorticosterone acetate injections cause a marked intensification of the adrenalin effect upon blood pressure (10). Animal experiments point in the same direction (11).

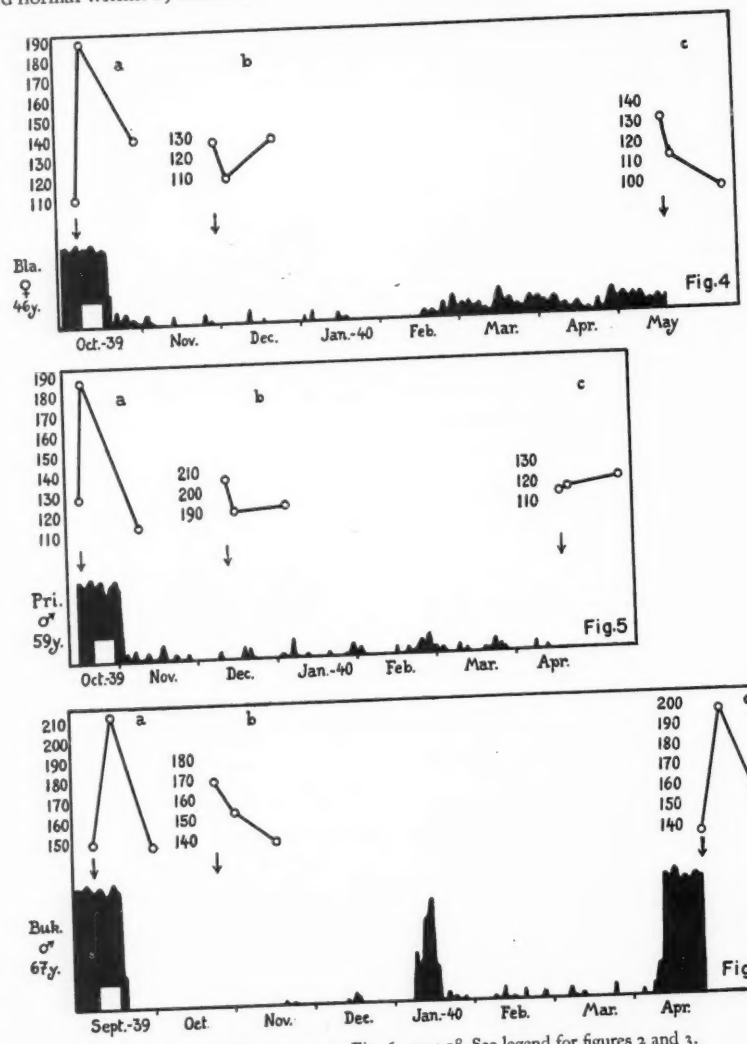

Fig. 4., *case 16*. Fig. 5., *case 20*. Fig. 6., *case 18*. See legend for figures 2 and 3.

In all instances of subjective improvement following roentgen irradiation of the suprarenal glands the above mentioned AC discharges after exercise disappeared, coinciding with the weakening or disappearance of the anginal attacks. In one case of a complete relapse the AC discharges reappeared in their original intensity after having been absent during a period of wellbeing of the patient.

In series of experiments on rats (12) it was found that the heart muscle absorbs larger amounts of parenterally injected adrenalin and desoxycorticosterone than other organs. Moreover the AC content of the heart muscle was spontaneously almost doubled and markedly enriched in adrenalin during physical exercise and during exposure to cold. These facts are in accordance with the teachings of physiology con-

cerning the discharge of adrenalin from the suprarenal glands under the circumstances mentioned and they correspond with the typical occurrence of anginal attacks during exercise and exposure to cold in patients with coronary sclerosis.

Pretreatment with thyroxin enhances intensely the absorption of injected adrenalin by the myocardium and of its toxic effect upon the heart. During the winter season the AC concentration of the heart muscle was found considerably higher than during the summer. The increase of cardiac disturbances during the winter months (13) may be due to the seasonal changes in the myocardial AC concentration. The therapeutic effect of thyroidectomy in angina pectoris (14, 15) is obviously to be ascribed to an elimination of the enhancing influence of the thyroid hormone upon myocardial adrenalin absorption.

TABLE 5. AC AND BLOOD PRESSURE LEVELS IN PATIENTS WITH ANGINA PECTORIS AT REST BEFORE AND AFTER X-RAY TREATMENT

Case	Before treatment		After treatment			
			4–6 wks.		5½–8 mo.	
	AC	B.P.	AC	B.P.	AC	B.P.
	color units/cc.	*mm.*	*color units/cc.*	*mm.*	*color units/cc.*	*mm.*
15	200	160/80	62	170/100	—	—
16	113	100/70	130	98/80	135	100/70
17	100	132/100	176	140/90	—	—
18	152	170/120	171	170/110	140	192/100
20	131	150/70	209	148/70	118	150/94
21	257	216/98	176	160/90	185	162/76
23	145	142/80	114	140/0	252	160/110
Average	157	153/88	151	147/77	166	153/29

The reappearance of anginal attacks in these cases, if thyroid treatment becomes necessary because of myxedematous features, is probably caused by a renewed intensification of adrenalin absorption by the heart, analogous to the findings in animals.

Roentgen treatment of the suprarenal glands, if successful, abolishes the abnormally intense secretory reaction to the sympathetic stimuli accompanying physical exercise, without impairing their normal routine activity. This protects the heart muscle, with nondilating coronary arteries, from sudden influxes of high anoxiating concentrations of suprarenal hormones. The specific anoxiating effect of adrenalin upon the heart muscle, which by far exceeds the increased oxygen consumption required for increased activity has been studied extensively by Gollwitzer-Meier (16) and Gremels (17).

The effect of the roentgen dosage as used in the treatment of angina pectoris consists merely in the abolition of an abnormal degree of secretory hyperirritability; very much larger doses would be required to produce structural damage to the suprarenal glands comparable to that obtained in animals through intense irradiation of these organs (18–21). In the suprarenal glands of 2 patients who had died from coronary occlusion at different intervals after

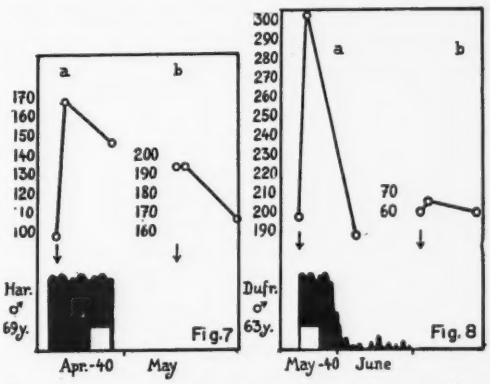

Fig. 7. *case 17.* Fig. 8, *case 15.* See legend for figures 2 and 3.

roentgen irradiation, no structural abnormalities were found.

During the past two years 34 angina patients were treated in Burlington, Vermont by Dr. A. B. Soule, Jr. and in other American cities under the medical supervision of the author. The results are about the same as those previously published in regard to the author's European material. Of the 34 American patients 74% were improved (36% completely or almost completely freed of complaints, 38% moderately to markedly improved, 26% unimproved). Each of these groups had received an average number of 1.3 series of treatments, thus considerably less than the European patients. The average duration of improvement up to the present is 8 months. In 8 cases there were temporary relapses.

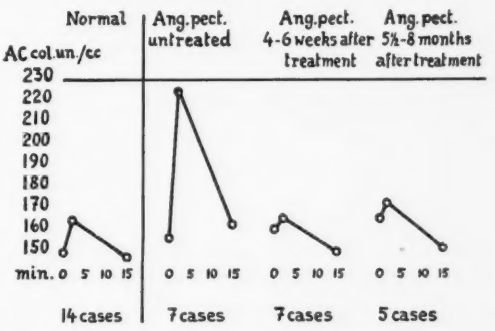

Fig. 9. AVERAGE CURVES OF THE BLOOD AC LEVEL REACTIONS TO EXERCISE IN NORMAL PERSONS AND IN THOSE WITH ANGINA PECTORIS BEFORE AND AFTER CLINICALLY SUCCESSFUL IRRADIATION OF THE ADRENAL GLANDS.

Similar favorable results were reported by Hadorn (22), by Schittenhelm (23) who recommends roentgen irradiation of the suprarenal glands in angina pectoris "under all circumstances," and by Lippross (24), who found it effective in otherwise intractable patients with angina pectoris.

The complete failure to respond to this treatment in a minority of the patients may be due to insufficient dosage and/or to the fact that adrenalin is produced not only in the suprarenal glands but also by the sympathetic neurones of the arterial walls and of the heart itself (25), where it appears under the influence of sympathetic stimuli. Thus it is quite conceivable that in some cases the depression of suprarenal discharges through local irradiation will not suffice to prevent adrenalin from other sources from acting upon the heart. Total irradiations might be considered in such cases.

Only recently the author has become acquainted with an article which was published in 1934 by Shambaugh and Cutler (26) in which these authors discuss the possibility of adrenalin discharges upon effort and emotion being involved in the mechanism of angina pectoris. Although this conception was expressed only hypothetically, it should be stated that Shambaugh and Cutler must be credited with having been the first investigators to clearly recognize the importance of suprarenal secretion in the pathogenesis of angina pectoris.

CONCLUSIONS

Adreno-cortical (AC) compounds, which consist of adrenalin combined with cortical sterols were quantitatively determined in the blood of individuals without and with angina pectoris by a chemical method.

In angina patients the blood AC level, although generally normal at rest, showed abnormally intense, sharp elevations after physical exercise. These elevations persisted for several minutes. The AC compounds which were discharged into the blood stream during physical exercise were particularly rich in adrenalin.

Therapeutic roentgen irradiation of the suprarenal glands, if successful, resulted in disappearance of the abrupt AC discharges on effort, coinciding with complete or almost complete disappearance of the subjective anginal symptoms for periods of several months.

The significance of these observations is discussed from the point of view of the theory that angina upon effort is caused by the specific anoxiating effect of sudden suprarenal discharges upon the heart muscle whose oxygen supply is inadequate due to sclerosis of the coronary arteries and their inability to dilate adequately.

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Therapeutic Use of Estrone Suspensions[1]

[Menopause]

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Natural estrogens are readily destroyed or inactivated by the liver, so that upon being rapidly absorbed from the site of administration their effect lasts only a short time. Retarding the rate of absorption results in an increased period of estrogen action which permits more desirable therapeutic effects. Absorption of estrogens into the blood stream may be delayed *a*) by chemical combination with fatty acids, *b*) by dissolving in a medium which is slowly absorbed, such as oil or wax, and *c*) by depositing the crystalline material directly into the tissues. With the last method there is a slower uniform rate of absorption over a much longer period of time than with an equal quantity of estrogen in solution since the crystals of estrogen have relatively small surface area and are only slightly soluble in tissue fluids (1).

For therapeutic purposes, implantation of pellets or crystals of estrogens appears to be a most efficient method of administration. Similar enhancement of results has been obtained with implantation of other steroids such as desoxycorticosterone and testosterone. Nevertheless, there is a certain amount of hesitation on the part of many physicians to use this method of administering estrogens which requires a special technic. We have therefore, utilized the principle of implantation of crystalline estrogens in a form which does not sacrifice the convenience or practicability of simple injections.

This dosage form consists of a suspension of estrone crystals in an aqueous medium. It is postulated that after injection into the tissues, the aqueous medium is rapidly absorbed leaving a deposit of crystals in the tissues to be absorbed slowly just as with implants. Laboratory experimentation revealed that the estrus induced in castrate rodents with such a preparation persisted for a much longer time than with similar quantities of estrone in oil solution or even estrone suspended in oil (2). The therapeutic efficiency of the aqueous suspension in the menopause was tested in the following experiment.

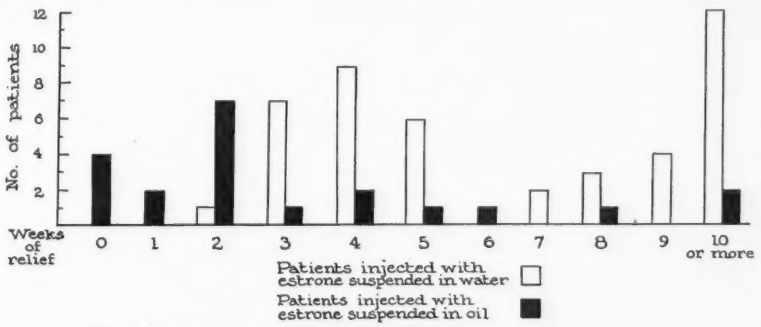

Fig. 1. Chart showing intervals of freedom from symptoms of menopause following last injection of estrone suspensions.

Methods and Results

An amount of estrone which was considered to be in considerable excess of the average amount necessary to relieve the symptoms of menopause was administered to a group of women displaying the typi-

Received for publication June 2, 1941.

[1] Read before the Association for the Study of Internal Secretions, May 3, 1941.

cal symptoms of this condition. Inasmuch as these symptoms and their relief by estrogen therapy have been repeatedly described in the literature, no detailed description of this phase will be attempted. The changes in the frequency and intensity of the hot flashes were used as criteria of relief, although the disappearance of other symptoms such as nervousness and sweats were included in the evaluation of the therapeutic success. The period in which patients were symptom-free without further treatment was taken as an index of efficiency of this preparation. In this manner, 5 mg. of estrone suspended in aqueous-gum acacia solution[2] was administered once a week for 3 weeks to a group of 44 patients with typical menopausal symptoms. For purposes of comparison, a control group of 21 women received, in a similar manner, injections of 5 mg. of estrone suspended in oil. This preparation was used in preference to an oil solution of estrone inasmuch as estrone is only slightly soluble in oil and it would require about 5 cc. of oil to convey 5 mg. of estrone in solution. This volume of material was considered unsuitable for injection. The chart in figure 1 illustrates the length of time following the last injection of the estrone preparations during which the patients were free of symptoms. Inasmuch as the return of the symptoms was usually gradual over a period of two or three days, it was considered sufficiently accurate to tabulate the periods in terms of weeks.

From this chart it can be seen that the therapy with aqueous suspension of estrone was superior to that with oil suspensions. Twelve of the 44 patients receiving aqueous suspensions were benefited for periods of 10 weeks or more. Only one was benefited for less than 3 weeks following the last injection. Four apparently had had no return of symptoms after 4 months. Of those receiving the oil suspension, 12 of 21 had relief for two weeks or less. Four of these 12 had slight or no relief.

TABLE 1. COMPARISON OF THE LENGTH OF PERIODS OF FREEDOM MENOPAUSAL SYMPTOMS AFTER INJECTION OF AQUEOUS SUSPENSION AND OF OIL SUSPENSION OF ESTRONE IN THE SAME PATIENT

Patient	Aqueous Suspension	Subsequent Oil Suspension
	wks.	*wks.*
1	3	No effect
2	3	Slight improvement
3	3	2
4	5	8
5	3	1
6	3	2
7	5	5
8	5	2
9	4	3
10	7	4
11	4	12
12	14	4
13	8	1
14	8	2
15	4	Slight improvement
16	3	2
17	4	2

In order to make a direct comparison of the efficiency of these two types of estrone suspension in the same patients, 17 of the 44 patients who received aqueous suspensions were subsequently treated with the oil suspension after the return of their symptoms. Table 1 contains the data on this series of patients, and indicates the comparative periods of freedom from symptoms in each patient.

It can be noted that 14 of the 17 patients treated with aqueous suspension were benefited for a significantly greater period of time than those treated with the oil suspension. Only two of the patients treated with the oil preparation were more greatly benefited than with the aqueous solution.

DISCUSSION

From these results and those obtained in laboratory animals which show that estrone suspended in oil is superior to estrone in oil solution but inferior to the aqueous suspension in inducing a protracted estrus response it is concluded that estrone suspended in water is more effective therapeutically than estrone in oil solution. Our results demonstrate that estrone suspended in water produces more prolonged relief from menopausal symptoms than similar quantities of estrone suspended in oil.

We consider that the estrone suspended in water behaves like implants of estrone crystals. It appears that the estrone suspended in oil is not as efficient an implant as estrone suspended in water. In the latter, the rapid absorption of the aqueous medium leaves an intact deposit of crystals in the tissues. With the estrone in oil preparation a considerable amount of estrone is dissolved in the oil. This estrone is absorbed relatively rapidly, and as this takes place, some of the estrone in suspension goes into solution in order to maintain the equilibrium of the estrone-oil system. Thus the effect of implantation is lost to a considerable extent.

We wish to call attention to our results in 12 of 44 patients treated with aqueous suspension who had relief for 10 weeks or more. It is doubtful that the estrone crystals were retained in the tissues for this length of time. It is more likely that, as Salmon, Geist and Walter (3) have postulated for estrogen implants, the slow uniform absorption of the estrogens allows for a physiological readjustment to estrogen deprivation amounting at times to an actual curing of the patient.

[2] Supplied by Abbott Laboratories, North Chicago, Illinois.

In addition to the enhanced therapeutic efficiency, another advantage in using aqueous suspensions of estrone over oil solutions, is the freedom from possible sensitivity reaction to the oil.

SUMMARY

The injection of estrone crystals suspended in water is superior to the injection of similar quantities of estrone crystals suspended in oil or estrone in oil solution in producing relief of menopausal symptoms and in prolonging the period of relief following cessation of injections. The injection of estrone crystals in water is considered equivalent to implanting estrone crystals directly into the tissues, without necessitating the special technic required for implantation.

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Oral Administration of Methyl Testosterone in Gynecology

[Androgens in Gynecology]

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THE USE OF ANDROGENIC HORMONES for the relief of varied functional gynecologic disorders has now been thoroughly accepted. That male sex hormone therapy has an established use in certain gynecologic disturbances is attested by the large number of clinical and experimental reports covering thousands of cases. The method of administration of these androgenic substances has been parenterally, either by the intramuscular injection of testosterone propionate in oil, the use of an active ointment through the skin, or more rarely, the subcutaneous implantation of pellets. The purpose of the present paper is to show that equally good results in the treatment of many gynecologic disturbances have been obtained by the oral administration of the synthetic and orally active androgenic hormone, methyl testosterone. It will be seen from the results of the present series of cases that the only therapeutic difference between the intramuscular injection of testosterone propionate and the oral administration of methyl testosterone is one of dosage. By the treatment of a varying group of gynecologic disturbances, using both products and comparing their potencies, it was determined that 30 mg. of methyl testosterone orally gave essentially the same clinical response as 10 mg. of testosterone propionate parenterally, that is, the equivalent dosage ratio of methyl testosterone to testosterone propionate is that of three to one. In all other aspects, both hormones act in exactly the same therapeutic manner.

INHIBITION OF LACTATION

22 Cases

Inhibition of lactation by the intramuscular injection of testosterone propionate has been reported by several investigators. Kurzrok and O'Connell (1) successfully produced inhibition of lactation in 19 of 21 puerperal women by the intramuscular injection twice daily, for 1 to 3 days, of 25 mg. of testosterone propionate. Siegler and Silverstein (2) found that 3 injections of 10 mg. each of testosterone propionate were adequately effective in 47 of their 50 cases. Birnberg, Kurzrok and Klor (3) reported the successful use of testosterone propionate in inhibiting lactation in 45 of 56 cases.

Early attempts by the writer to prevent lactation by the oral administration of methyl testosterone met with failure, in spite of relatively large doses used. It was not until Duffy and Corsaro (4) called attention to it that the writer realized the importance of the time factor in the administration of methyl testosterone for a successful outcome in inhibiting lactation. It was shown by the above authors that a dose of 50 to 75 mg. of testosterone propionate was effective in suppressing lactation in all cases (25) in which it was administered at the beginning of lactation, that is, on the 3rd or 4th day after delivery. But when the same quantities were injected immediately postpartum or after lactation had been established for sometime, they were without effect. An explanation of the mechanism involved in the above-mentioned time factor in the use of testosterone products has been advanced by the authors as follows. After delivery there is a rapid withdrawal of the estrogenic factors which have acted throughout pregnancy as inhibitors of the hypophysis. Freed from these inhibitory factors, the anterior lobe of the pituitary gland undergoes increased function with the production of lactogenic hormone, which in turn stimulates the secretion of the mammary ducts with the initiation of lactation on the second or third day following delivery. The continuation of this lactation is dependent on suckling (peripheral stimulation), as shown by the work of Selye (5). Thus the most effective time for the administration of testosterone to suppress lactation would be following the removal of the estrogenic factors and before regular lactation had been established by lactogen and suckling. This has been found to be in the majority of women about 48 to 72 hours following delivery, and it is truly at this time that inhibition of lactation can be most successfully produced by the use of androgenic products and notably (at this time) with relatively small doses.

Similarly, to inhibit lactation in a second group of cases Duffy and Corsaro found that methyl testosterone given orally, in doses of 25 mg. at intervals of 4 hours or 3 times a day for 6 doses, produced results comparable to those obtained with 50 to 75 mg. of testosterone propionate administered subcutaneously. Of importance was the fact that methyl testosterone was given at the beginning of lactation, that is, on the 2nd or 3rd day after delivery.

Received for publication August 20, 1941.

Following the above procedure, a group of 22 puerperal patients were given 30 mg. of methyl testosterone[1] orally every four hours (3 times a day) for two days, beginning at the time of the earliest signs of lactation, usually the 3rd or 4th (occasionally the 2nd) day postpartum. In all, 180 mg. of methyl testosterone was used in each case. There was complete inhibition of lactation in 20 of the 22 cases (90%). Two patients did not respond to the above amount, but on repetition with one-half the dosage one ceased lactating while the other showed no response to additional therapy. Tight breast binders, catharsis and rigid limitation of fluids were purposely omitted and were found not to be required.

It will be noted (as in the report of Duffy and Corsaro) that 180 mg. of methyl testosterone orally produced results similar to those obtained by the injection of 50 to 75 mg. of testosterone propionate, giving a dosage ratio of methyl testosterone to testosterone propionate of three to one.

POSTPARTUM ENGORGEMENT OF BREASTS

12 Cases

In a small group of 12 cases in which postpartum engorgement or congestion of the breasts was found to be excessive and annoying, and where inhibition of lactation was not desired, methyl testosterone was administered in smaller dosage. A dose of 20 mg. three times a day for 2 or 3 days was followed by relief of the congestion and softening of the breasts in 10 of the 12 cases. Nursing of course was continued (as is desirable) during therapy, and no noticeable diminution of an adequate milk supply was evident. To the contrary, it appeared that the babies suckled with more ease as the mammary tension was released with resultant increased facility in the flow of milk.

In neither of the above groups (inhibition of lactation or engorgement of the breasts) did mastitis or breast abscess develop. As treated not so long ago with tight breast binders, marked fluid limitation and purging, at least the presence of one or more breast abscesses would not have been surprising in the course of events.

Table 1. Summary of Cases and the Dosage of Methyl Testosterone

	No. of Cases	Dosage	Successful Results No.	%	Partial Relief No.	Failure No.
Inhibition of lactation	22	90 mg. daily for 2 days, beginning 48 to 72 hr. postpartum	20	91	1	1
Postpartum engorgement of breasts	12	60 mg. daily for 2 to 3 days	10	83	0	2
Afterpains	3	50 mg. immediately after delivery	3	100	0	0
	4	50 mg. during labor, prophylactically	3	75	1	0
	2	50 mg. on 2nd day postpartum	0		0	2
Dysmenorrhea	16	30 mg. daily for 2 wk. preceding menstruation	12	75	1	3
	4	100 mg. daily for 1 wk. preceding menstruation	3	75	1	0
Dysmenorrhea plus endometriosis	3	30 mg. daily for 2 wk. preceding menstruation	0		1	2
Premenstrual tension and mastalgias	12	30 mg. daily for 2 wk. preceding menstruation	7	58	3	2
Menopause	14	30, 40 or 50 mg. daily depending on no. of flushes and severity of symptoms	11	79	2	1
Menopause, resistant to estrogens	3	30 mg. daily for 2 to 3 wk.	2	67	1	0
Functional uterine bleeding	11	30, 40 or 50 mg. daily depending on severity	11	100	0	0
			(two pregnancies ensued during therapy			

DYSMENORRHEA

23 Cases

The use of testosterone propionate in the treatment of dysmenorrhea has been reported with varying success by a number of workers. Salmon, Geist and Walter (6) treated 30 women, who complained of severe dysmenorrhea, with testosterone propionate in dosages of 10 to 50 mg. in divided doses 3 times a week throughout the cycle. Good results were obtained in 26 of the 30 patients. That the beneficial effect of testosterone propionate not seldom continues after cessation of therapy was shown by Greenhill and Freed (7, 8) who reported freedom from dysmenorrhea as long as one year after discontinuance of therapy in 50% of their cases. Rubinstein and Abarbanel (9) found that most of their cares of essential dysmenorrhea responded satisfactorily to injections of testosterone propionate in relatively small doses (15 mg. the week before onset of menstruation), and believed that relief resulted from a lowering of estrogenic and gonadotropic levels (consequent upon androgenic therapy) with a resulting decrease in painful uterine contractions. Mandy and Mandy (10) in a series of 21 cases treated with testosterone propionate in dosages of 15 to 50 mg. one week

[1] The methyl testosterone (Neo-Hombreol M) used in all cases in this paper was supplied through the kindness of Dr. Leo A. Pirk of Roche-Organon, Inc., Nutley, N. J.

before menses obtained relief as follows: complete in 16, partial in 4, and no response in one patient.

The use of methyl testosterone orally for the relief of dysmenorrhea was first reported by Foss (11). Three patients with dysmenorrhea were given 10 mg. of methyl testosterone daily, two of whom received it for 14 days before menstruation without improvement; the third was treated in the middle of the cycle with complete relief.

In the writer's series of 16 cases of dysmenorrhea in patients ranging in age from 14 to 44 years, with no discernible pelvic pathology, successful relief was obtained in 12 patients (75%) by the administration of 30 mg. of methyl testosterone daily for 2 weeks prior to menstruation. One patient had partial relief while three others in no way responded to therapy and were also not relieved by androgen or progesterone parenterally.

Of 4 additional cases (aged 16, 17, 27 and 32 years) receiving 100 mg. a day throughout the week preceding menstruation, 3 reported good results and one fair. In 3 cases of dysmenorrhea associated with endometriosis (two previously operated upon) no relief was obtained in 2, while only slight lessening of discomfort was noted in the third.

AFTERPAINS

9 Cases

The relief of dysmenorrhea by the male sex hormone, probably on the basis of inhibiting uterine muscular action, suggested the possible similar relief of afterpains. Thus, Abarbanel (12) was able to report that in 82% of 49 patients afterpains were relieved by the injection of 10 mg. of testosterone propionate soon after delivery. Likewise, in 88 of 100 women who also received testosterone propionate in a 10 mg. dose at or near the time of delivery (prophylactically), no afterpains were evident.

In our attempts to relieve afterpains in a small series of 9 patients treated with methyl testosterone, the time factor in administration of the hormone again proved of interest. In 3 cases 50 mg. was given shortly after delivery and repeated the following day, with complete absence of afterpains resulting. In a group of 4 multiparous patients who had had severe afterpains in previous deliveries, 50 mg. was given during labor (prophylactically), with failure of afterpains to appear in 3 patients and only slight discomfort experienced by the fourth. But when 50 mg. was given to each of 2 patients on the second day postpartum no relief of established afterpains was noticed. It thus appears that in this small series of cases afterpains can be prevented more readily by the prophylactic administration of methyl testosterone during labor or immediately following delivery than they can be relieved once definitely established. Parenthetically it might be added, that the hormone when given prior to delivery in no way interfered with the normal progress of labor.

PREMENSTRUAL TENSION AND MASTALGIA

12 Cases

Since mastalgias and premenstrual tension are probably due to an increased estrogen content of the blood it appears that the androgens, by their estrogen-negation action, should decrease these phenomena. It was shown by Demarest and Capitaine (13) that fairly though not uniformly successful results were obtained in the relief of premenstrual tension and mastalgias by the intramuscular injection of testosterone propionate. Their failure to obtain relief in a larger percentage of patients was probably due to the small quantity of hormone used, 5 mg.

Twelve patients complaining of mastopathia premenstrualis (associated in the majority with a feeling of tension, nervousness and irritability) were treated with methyl testosterone. Thirty mg. was given daily during the 2 weeks prior to menstruation with the following results: complete (subjective) relief in 7, partial relief in 3, no effect in 2. Thus, by the administration of 420 mg. of methyl testosterone orally in the latter half of the cycle, 10 of the 12 patients were completely or partially relieved of their premenstrual breast and generalized tension. In only one instance was there a disturbance in menstruation (diminished). It thus appears that in the treatment of premenstrual tension as well as that of dysmenorrhea, methyl testosterone in dosages insufficient to produce disturbances in the natural menstrual flow, will give relief in a large percentage of cases.

MENOPAUSE

14 Cases

It has been shown repeatedly that just previous to and following the menopause there is a progressively diminishing content of estrogenic substances in the blood and urine. Associated with this is an increase of blood gonadotropic hormone from the adenohypophysis, resulting probably from the lack of inhibitory action on the pituitary by the reduced quantity of estrogen. As the concentration level of blood estrogen is reduced, psychic, nervous and other manifestations, usually referable to the sympathetic system, appear.

The use of estrogenic hormones in the relief of menopausal disturbances has been well established by numerous reports (14, 15, 16) as well as in the daily practice of many physicians. That androgenic substances might have a similar effect by their property of inhibiting the adenohypophysis (with a consequent reduction of gonadotropic hormone) was first reported by Mocquot and Moricard

(17). These authors used the male sex hormone in the treatment of climacteric disturbances (following bilateral oöphorectomy) with satisfactory results. Larger series of cases were reported by Birnberg, Kurzrok and Livingston (18, 19) who, in the second of these reports, treated 21 women by the injection of 30 to 50 mg. of testosterone propionate weekly with complete relief of menopausal headaches, flushes and sweats. No failures were reported and they were able to administer tesotsterone propionate to some women who could not tolerate or were refractory to estrogens.

The present writer treated 14 patients (aged 37 to 48 years) suffering from menopausal disturbances with methyl testosterone orally. None of the women in this series had previously had any type of hormone therapy. The cases could be divided roughly into 3 groups according to the number of flushes (plus generalized subjective disturbances). There were 8 mild cases, two moderate and four severe, with 1 to 2, 4 to 6, and 8 or more flushes per day respectively. Treatment consisted of the oral administration of methyl testosterone in the following manner: 30 mg. a day throughout the month for the mild cases, 40 mg. for the moderate and 50 mg. for the severe cases. Results: in 8 mild cases there was complete relief in 6, partial in 1, no effect in 1; in 2 moderate cases there was complete relief; in 4 severe cases there was complete relief in 3 and partial relief in 1. Thus 80% (11 of 14 in this small series) were completely relieved of their flushes. Associated phenomena such as headaches, sweats, subjective nervousness, excitability and irritability and disturbances of sleep, were all either eliminated or improved to such degree that the patient no longer considered them as disturbing factors. It will be noted, however, that the above dosage schedule was large—approximately 900 mg. of methyl testosterone per month in the mild cases, 1,200 mg. in the moderate and 1,500 mg. in the severe cases. At the ratio of three to one (methyl: propionate) this would correspond to 300 to 500 mg. of testosterone propionate per month, which as shown by Birnberg et al. (18) is well above the amount of androgenic substance required to produce complete relief in their 21 cases of menopausal disturbances. It might here be stated that several of the above 14 climacteric patients were treated prior to any known relationship of the potency of methyl testosterone to testosterone, and consequently relatively large doses were tentatively and experimentally used. A further series of patients being treated at the present writing appears to show that satisfactory results are being obtained by the administration of 10 to 20 mg. a day in the mild and 20 to 30 mg. in the more severe cases of menopausal distress.

One patient (receiving 50 mg. a day for a period of 2 months, 3,000 mg. in all) showed signs of masculinizing effect—hirsutes of lip and chin, increased libido and congestion and hypersensitiveness of clitoris. Maintenance of the patient at a lower dosage over a period of 3 months resulted in disappearance of the hirsutes, but no change was noted by the patient in the augmented libido.

Repeated vaginal smears taken during and after therapy failed to show a change from the picture of menopausal estrogen deficiency. There were leukocytes with small atrophied cells. It was apparent, as with the estrogens (16), that relief of menopausal disturbances could be obtained without a change in the vaginal smear or before such changes appeared.

Three menopausal patients were treated who had previously received estrogenic hormone in large doses without effect—apparently showing a refractoriness to estrogens. One patient (aged 42 years) had been complaining of various menopausal disturbances since her physiologic amenorrhea 3 years previously. Of the other 2 patients (both aged 36 years) one had undergone operative castration (bilateral ovariectomy), the other radium castration for metrorrhagia. The administration of 30 mg. per day resulted after 2 to 3 weeks of therapy in complete cessation of climacteric complaints in 2 of the patients and marked improvement in the 3rd (radium case). Whether androgenic substances will be able to replace the estrogens in those patients who are either refractory or allergic to the latter, must await further investigation. The administration of androgenic hormone is decidedly to be preferred to the estrogens in the treatment of natural or artificial menopause in patients who have had extensive endometriosis or other new growths (20). In such a patient, or in one with android characteristics, the menopausal symptoms could be relieved by the male sex hormone, avoiding at the same time the growth-stimulating effect of the estrogens.

FUNCTIONAL UTERINE BLEEDING

11 Cases

It seemed only natural that a potent androgenic substance, once produced, would find a major gynecologic use in the attempt to control uterine bleeding of the functional type. The male sex hormone, of all its uses in the female, has found its widest scope in the treatment of functional uterine hemorrhage. That this has met with a high degree of success has been shown by several reports, among which is that of Gaines, Salmon and Geist (21) in which 24 of 25 women were relieved of functional uterine bleeding by the intramuscular use of testosterone propionate in dosages of 300 to 1,000 mg. per month. By the injection of 300 to 2,000 mg. of testosterone propionate (the latter amount used experimentally and by no means advised routinely) Foss (22) not only inhibited uterine flow but produced an atrophy of the endometrium. Green-

hill and Freed (8), as well as Mazer and Mazer (23) have found that 250 to 500 mg. of testosterone propionate monthly in divided doses was required to alleviate functional bleeding in most women. That smaller doses of testosterone propionate are often successful in a percentage of patients has been shown by Sturgis (24) and his associates who found that menometrorrhagia was lessened by as little as 10 to 30 mg. and stopped by 10 to 120 mg. Rubinstein (25) also cited a case of bleeding which was controlled by 5 mg. of testosterone propionate twice weekly. These latter reports are exceptional in the small amount of hormone used, for usually 150 to 250 mg. (occasionally 400 to 500 mg.) of testosterone propionate is required for control of the average case of functional uterine bleeding.

Of the 11 patients in this category treated by the oral administration of methyl testosterone, 5 had menorrhagia and 6 menometrorrhagia. Excluding one case of menometrorrhagia which had associated multiple fibromyomata in a uterus the size of a 3-month pregnancy, no demonstrable pelvic organic pathology was discernible in the group. Diagnostic curettement or endometrial biopsy was done on 8 patients, but the findings were equivocal, the majority showing the normal proliferative or secretory structure of the endometrium depending on the time of endometrial examination in relation to ovulation. In only two instances was there an evident endometrial hyperplasia (hyperestrogenic). There was no apparent relationship between the microscopic endometrial picture and the amount or duration of the bleeding. This lack of correlation between the histologic picture and the clinical findings has been mentioned by several writers, particularly Hamblen (26).

Since at this time an exact or even an approximate relationship between the potency of methyl testosterone and testosterone propionate had not been reached, the doses used were again of the 'trial and error' type. In one of the early cases of menometrorrhagia (not included in the present series) 100 mg. was given daily for a period of 2 months, which resulted in complete absence of bleeding for the next 102 days. This patient received 3,000 mg. of methyl testosterone per month, which at the present determined ratio of three to one is equivalent to 1,000 mg. of testosterone propionate. It was noted that, in spite of the massive dosage of methyl testosterone used (6,000 mg. in 60 days), there were no signs of virilism such as enlarged clitoris, hirsutes, acne or deepening of the voice. This appears to be in contrast to what one might expect with a corresponding dose of testosterone propionate (2,000 mg.). A similar finding has been noted by Salmon (27) who observed that in a series of 46 women treated with methyl testosterone, hypertrichosis was distinctly less frequent than in those treated with testosterone propionate. He goes on to say that: "If this lower arrhenomimetic potency is confirmed in a larger series of cases, it would make methyl testosterone more valuable as a gynecologic therapeutic androgen than testosterone propionate."

The 5 patients with menorrhagia and one with mild menometrorrhagia received 50 mg. of methyl testosterone daily throughout the month, 1,500 mg. per patient. Menorrhagia in all cases was completely checked, and in 2 patients menstruation did not return for 52 and 60 days respectively. Subsequently a reduction to 30 mg. per day (800 to 900 mg. per month) was followed by normal menses in each instance. At present the bleeding in all of these patients is under control by the daily intake of 20 to 30 mg.

In the remaining 5 cases of menometrorrhagia, 30 mg. daily resulted in marked benefit to all patients. Intermenstrual bleeding ceased with diminution in the menstrual flow soon after therapy was begun. Three patients have had essentially normal menstrual periods during the last 3 months with a maintenance dose of 20 to 30 mg. daily. The remaining 2 patients, after 2 normal menstruations each, missed their subsequent period. It was at first believed that the androgenic dosage was excessive, but further examination, confirmed by Aschheim-Zondek tests, revealed the presence of pregnancy in both instances. The patients had been married 2 and 5 years respectively and neither had previously conceived.

In order to compare further the potencies of methyl testosterone and testosterone propionate, 2 patients (not in the above series) suffering from menometrorrhagia and kept under control with 250 mg. of testosterone propionate were placed on methyl testosterone. It was found that 30 mg. daily throughout the month exclusive of the days of the menstrual period resulted in strikingly similar control of the bleeding. A trial elimination of all therapy for a period of 2 months resulted in a return of menometrorrhagia in both patients. Thus approximately 750 mg. of methyl testosterone had the equivalent potency of 250 mg. of testosterone propionate, or in the ratio of three to one. This ratio, which corresponds consistently to the relative dosages as witnessed in the treatment of the gynecologic conditions including inhibition of lactation, menopause and dysmenorrhea appears to be definite.

SUMMARY

Methyl testosterone orally can be substituted for testosterone propionate parenterally in all gynecologic disturbances which show a therapeutic response to the male sex hormone.

Methyl testosterone by weight is one-third as effective orally as testosterone propionate parenterally; 30 mg. of methyl testosterone by mouth are

therapeutically equivalent to the injection of 10 mg. of testosterone propionate.

Signs of virilism appear less frequently with methyl testosterone than with testosterone propionate in proportionate dosage.

There were no untoward effects of methyl testosterone therapy, excluding the occasional complaint of slight gastric distress which was readily relieved by alkaline medication.

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Patterns of Uterine Motility

In the Normal Ovulatory and Anovulatory Cycle, after Castration, Coitus and Missed Abortion

[Uterine Motility]

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THE HUMAN UTERUS IS AN ORGAN designed for the purpose of reproduction. All of its physiologic activities which are under the influence of the hormones of the ovary and its anatomical relationships serve this end. To prepare for the fertilized ovum, aid in its implantation, nurture it until viability, and expel it when capable of independent existence, these are the functions of the uterus. That these desiderata may be accomplished some mechanism operates to produce a flaccid uterus during gestation and later reverse itself so that contractions occur and expel the fetus. Some knowledge of this control of motility may be gleaned from a study of the non-pregnant uterus. In the non-gravid state this organ undergoes cyclic changes in its endometrium (1) well studied in recent years by numerous investigators; cyclic changes in its vascular system, (2, 3, 4), studied by Markee on corneal transplants of endometrium in the macaque; and cyclic changes in the myometrium now under consideration by several investigators in this country and abroad (5–17).

Blair observed in 1922 that the motility of excised rodent uteri varied with the phases of the estrous cycle (18). Later it was observed that human uterine muscle fibers were capable of intrinsic motility only after adolescence and before the menopause. This intrinsic motility is abolished by oöphorectomy (19). These observations in animals and humans were made for the most part on isolated muscle in Ringer's solution and led to the conclusion that uterine contractions depend upon a secretion of the ovary.

Allen and Doisy in 1923 observed the changes in vaginal epithelium and uterine growth brought about by the injection of follicle fluid from the sow (20). Doisy in 1929 found a crystalline substance in the urine which had estrogenic properties (21) and it was soon learned that this was the excretion product of an ovarian hormone which would promote the growth and motility of smooth muscle fibers of the uterus. Now we know that there are a number of sterols, endogenous and exogenous, which have estrogenic properties.

In 1928 Corner and Allen demonstrated the progestational changes in the endometrium of castrated rabbit uteri by injection of alcoholic extracts of corpora lutea (22). Soon the inhibitory action of progesterone on uterine muscle was demonstrated. Smith and Engle (23) showed that maturation and rupture of the follicle was dependent upon a gonadotropic principle from the pituitary.

With these fundamentals adequately confirmed, it has been possible in recent years to accurately describe the cyclic changes in the endometrium, its spiral arteries, and the changes in the motility of the myometrium in relationship to the cyclic hormone changes from the ovary and pituitary. In the study of uterine motility the names of Knaus, Reynolds, Lackner, Moir, Robertson, Adair, McClellan, Kurzrok, and others are prominent. Kurzrok has recently described the patterns of motility in the normal non-gravid uterus. The work reported in this paper confirms certain of his observations.

Motility of uterine muscle may be studied by suspending excised strips in Ringer's solution. When the uterus is removed at different phases of its cycle or when it is removed during pregnancy or the puerperium, the muscle strips may be suspended in saline, contractions recorded, and the effect of drugs placed in the bath may be studied. Objections to this method are those which apply to all "in vitro" experiments.

Motility may be determined by direct palpation with the examining finger and Dickinson has reported upon the cyclic changes in myometrial contractility by such palpation (24). That the sense of touch may be developed to a marked degree is apparent to anyone who has visited the Carnegie Institute in Washington and seen the accuracy with which the investigators there determine the time of ovulation

Received for publication August 7, 1941.

in monkeys by rectal palpation. Nevertheless, there is some doubt as to the ability of the average worker to determine the type of uterine contractions in the human by digital palpation. External hysterography may be satisfactory in the early puerperium, but it is not practical at other times. Electrometric methods are now being investigated for the study of this problem.

TECHNIC

The intrauterine balloon, connected through a closed water system with a mechanical ink writer appears to be satisfactory and was used in this work (fig. 1). The tracings were recorded on the electric kymograph equipped with a timer. For study of the non-gravid uterus a small condom balloon attached to a flexible metal tube was inserted into the uterine cavity and the balloon distended with water (fig. 2). This was then connected through a closed water system to the ink writer. Pressure in the system was carefully maintained between 30 and 40 mm. Hg. by a U tube cut into the system. In the puerperal uterus a larger balloon was used and 70 to 90 cc. of water was usually required to distend the balloon.

Objections to the intrauterine balloon have been raised on the basis that a foreign body distending the uterus sets up contractions. This objection is valid because such is the case. I have often observed that, with the balloon in place and the pressure at 20 mm. or less, no contractions could be recorded. However, with the pressure kept between 30 and 40 mm. this method does provide a means of studying relative changes in the contractility of the human uterus in situ. Knowing what is to be expected from the uterus under certain standard conditions, it becomes possible to observe changes from the norm induced by certain external agents, and also to record its variations during the menstrual cycle. It has been possible to demonstrate in the uterus of a castrate woman that no amount of distention with the balloon will stimulate contractions unless the myometrium has been sensitized by estrogen. In spite of its experimental limitations, the technic here described appears to be the best now available for studying the motility of the human uterus in situ.

Normal Ovulatory Cycle

In the normally menstruating woman during the first half of the cycle, the uterus is under the influence of the estrogen elaborated by the maturing Graafian follicle. This estrogen dominance produces a rather characteristic pattern of uterine motility. The contractions are frequent, two to three a minute, their amplitude is relatively low and somewhat variable (fig. 2, 3). This type of contraction is initiated soon after the cessation of the menses and occasionally even before the menstrual flow stops. The same pattern is maintained until the time of ovulation. We have not been able to show any marked increase in uterine irritability just before or at the time of ovulation. At this writing 10 cases have been studied. All of them have been menstruating at fairly regular intervals. The motility recorded in each case during the follicular phase of the cycle has given the characteristic pattern shown in the tracings.

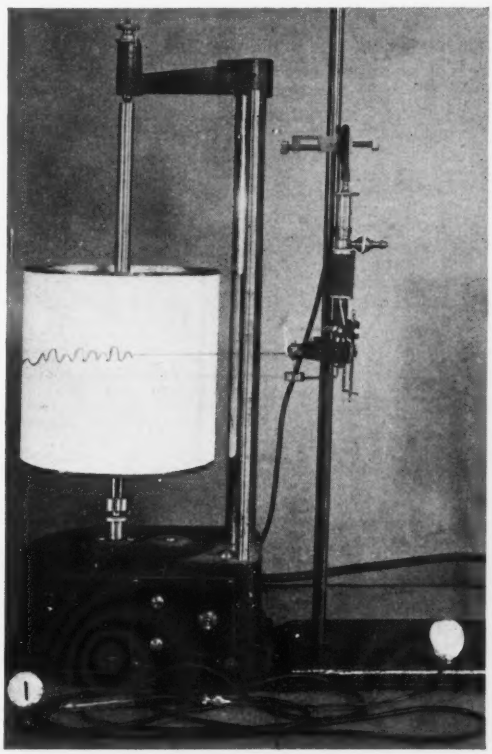

Fig. 1. THE BALLOON CONNECTED to the mechanical ink recorder and the electric kymograph.

During the latter half of the cycle the uterus comes under the influence of both estrogen and progesterone. The presence of a corpus luteum was demonstrated during the later part of the cycle by obtaining in every case a biopsy of the endometrium utilizing the suction technic. Records of uterine motility during the luteal phase shows a pattern distinctly different from that seen in the follicular phase. It must be remembered that during this phase even larger amounts of estrogen are being secreted than during the early phase plus progesterone from the corpus luteum. This hormone modifies the estrogen influence on the myometrium, but it did not completely abolish this influence. Progesterone inhibited the rate of contractions.

The average was reduced from 2 to 3 per minute to about one per minute, but the amplitude was greatly increased and the periodicity was much better established. The characteristic pattern of motility during the luteal phase is shown on the tracings. These were taken on the same 10 patients previously studied during the follicular phase.

Anovulatory Cycle

One patient has been under observation over a period of years for primary sterility. Repeated studies on this cycle was likewise confirmed by the presence of proliferative endometrium throughout.

Motility Following Castration

A patient, age 34, was operated upon in February 1941 for bilateral pyosalpinx and bilateral oöphoritis. Both ovaries and tubes were removed. Six weeks postoperative motility studies were made and the tracings showed a quiescent uterus. No contractions could be elicited even when the pressure in the balloon was raised to 80 mm. Hg (fig. 5). The studies

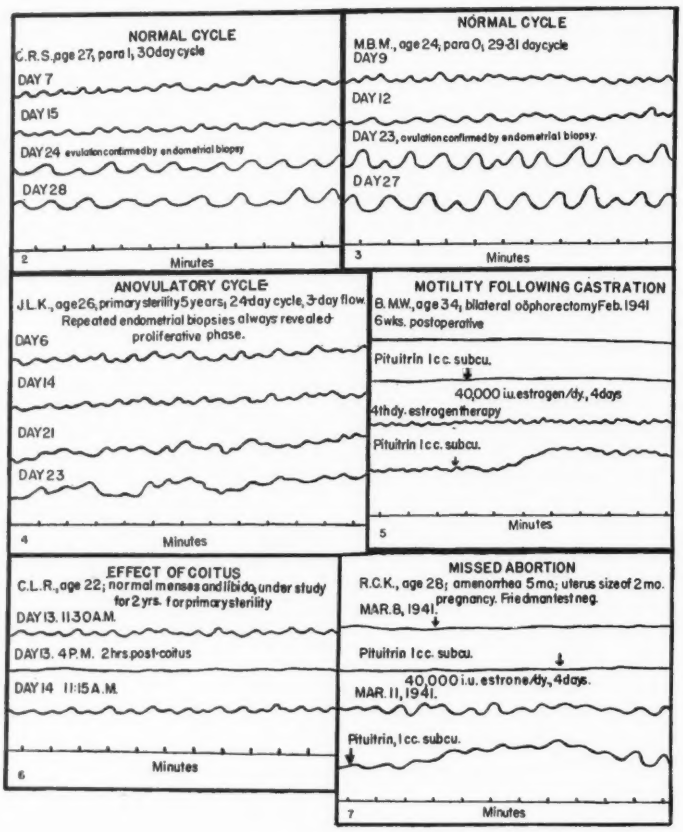

Fig. 2–7. Kymograph records of uterine motility in human female.

her endometrium during these years have never revealed a secretory phase, yet she bleeds at approximately 24-day intervals. This patient represents a case of anovulatory cyclic bleeding. The uterine tracings are shown in figure 4. Motility during the first part of her cycle was what one would expect under normal estrogen influence. However, this pattern of motility persisted throughout her cycle. In the latter half there was a certain degree of tetany apparent which can probably be explained on the basis of uninhibited estrogen influence. Absence of ovulation in were usually made with 35 mm. Hg. At this time the vaginal smears, stained according to the technic of Papanicolaou (25) showed the characteristic absence of keratinized epithelium. No contractions followed the administration of 1 cc. of pituitrin subcutaneously. The patient was given estrogen in the form of mixed natural estrogens[1] 10,000 I.U. daily for 4 days. On the 4th day intrinsic motility was demonstrated in the uterus, and a tetanic response followed 1 cc. of pituitrin subcutaneously. There are many questions

[1] Amniotin, E. R. Squibb & Sons, New York City.

which present themselves in this connection and these are now under consideration. How soon after oöphorectomy does the uterus lose its intrinsic motility? What is the minimum dose of estrogen required to restore it? Does the uterus after castration lose its ability to recover under estrogen administration?

Motility after Coitus

It has been observed in the rabbit that intrinsic uterine contractions are inhibited by coitus (26). A patient who was under observation for primary sterility presented herself as a suitable candidate for study of this phenomenon in the human. A tracing was taken on the 13th day of her cycle at 11 A.M. She was advised to have coitus about 2 P.M. and return for another study at 4 P.M. She agreed to do this and the results are graphically shown (fig. 6). The normal estrogen type of contractions were recorded in the morning tracing. The tracing made at 4 P.M. showed a quiescent uterus. The third tracing done on the following morning showed a return to normal intrinsic motility.

Motility In Missed Abortion

Mrs. C. L. K., age 28, menstruated last on Sept. 2, 1940. She was examined in December and a normal 11-week pregnant uterus was palpated. During December the patient had some bleeding which was controlled after 2 weeks of bed rest. She received 25 mg. of progesterone during this episode. On February 26th the uterus had apparently not increased in size and a Friedman test was reported as negative at this time. The test was repeated and again reported as negative. A diagnosis of missed abortion was made. The motility study was started on March 8th and a quiescent state of the uterus recorded on the tracing (fig. 7). The uterus did not respond to pituitrin. Estrogen was started and 40,000 I.U. of natural estrogen[1] was given daily for 4 days. Intrinsic motility was established on the 4th day and a tetanic response followed 1 cc. of pituitrin. A macerated fetus was subsequently expelled.

SUMMARY

The hormone cycle regulating human uterine motility has been reviewed. An intrauterine balloon connected through a closed water system to a mechanical ink recorder has been described as a means of studying motility in the uterus, and the sources of error in this technic emphasized. Patterns of uterine motility in the normal uterus showed a characteristic low amplitude, high frequency, somewhat tetanic type of contraction during the follicular phase. The contractions had a higher amplitude, lower frequency, and no tetany during the luteal phase. In a case of anovulatory cyclic bleeding the follicular type of contractions persisted throughout the cycle. The uterus of a castrate woman was quiescent and insensitive to pituitrin; its intrinsic motility and sensitivity to pituitrin was restored by estrogen. Coitus temporarily abolished the intrinsic motility of the uterus. In a case of missed abortion with a negative Friedman test the uterus was quiescent and insensitive to pituitrin, spontaneous motility was induced by estrogen and the sensitivity to pituitrin re-established.

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ASSOCIATION NOTICE

Announcement of the Annual Meeting

THE TWENTY-SIXTH ANNUAL MEETING of The Association for the Study of Internal Secretions will be held in Atlantic City, New Jersey on Monday and Tuesday, June 8th and 9th, 1942. The Hotel Traymore will be the headquarters for registration and for the scientific and business sessions. Room reservations should be made early with the Hotel Traymore.

The Chairman of the Local Committee is Dr. Matthew Molitch, 705 Pacific Avenue, Atlantic City, New Jersey.

PRESENTATION OF PAPERS

1. The title of the paper, and a comprehensive abstract must reach the President, Dr. Edgar Allen, 333 Cedar Street, New Haven, Connecticut, not later than April 10, 1942.

Abstracts submitted should be in proper form for printing in the program. Not more than the first 200 words can be included in the printed abstract.

2. Non-members who wish to present papers must have their titles and abstracts introduced by members.

3. The abstracts of papers will be considered by the program committee and the final program announced about May 10th, 1942.

4. Papers will be limited to ten minutes for presentation. A ten-minute presentation is designed for condensed discussion of new investigations, either in laboratory or clinical phases of endocrinology. Previous publication or presentation before other societies of national membership may be cause for omitting a paper from the program.

5. Papers presented at the Annual Meeting may be submitted for publication to the Editor of ENDOCRINOLOGY or THE JOURNAL OF CLINICAL ENDOCRINOLOGY. Such submission is invited. Acceptance of a paper for the program does not necessarily mean its acceptance for publication.

You are invited to bring this announcement to the attention of your colleagues and associates who have endocrine research in progress.

NOMINATION OF OFFICERS

The By-Laws of the Association provide that nominations for all elective offices shall be made by a Nominating Committee and forwarded to the Secretary at least sixty days before the annual meeting. The Nominating Committee for the current year, appointed by the President and accepted by the Council, is as follows:

Dr. Earl T. Engle, *Chairman*, College of Physicians and Surgeons, 630 West 168th Street, New York City.
Dr. E. L. Sevringhaus, Wisconsin General Hospital, Madison, Wisconsin.
Dr. E. C. Kendall, 627 Eighth Avenue, S. W., Rochester, Minnesota.

The By-Laws also provide (Article V, Section 2) that "Any member of the Association may submit nominations to the Nominating Committee for its consideration." Nominations may be sent to the chairman, Dr. Earl T. Engle, before March 1st, 1942.

The terms of the following officers expire at the time of the annual meeting in Atlantic City in 1942.

President-Elect	E. Kost Shelton
Vice-President	E. M. K. Geiling
Secretary-Treasurer	Henry H. Turner

Council Members	*Publication Board*
David P. Barr	David P. Barr
John C. Burch	Oscar Riddle
E. C. Kendall	

THE E. R. SQUIBB & SONS AWARD

The E. R. Squibb & Sons award of $1,000.00 was established in 1939, and given first in 1940 to Dr. George W. Corner, and in 1941 to Dr. Philip E. Smith. A special committee of five members of the Association chooses an investigator or investigators in the United States or Canada for one of the best contributions to endocrinology. Nominations for the award in 1942 by members of the Association may be sent to the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma not later than March 1st. The nomination should be accompanied by a statement concerning the nominee's contributions to endocrinology and a bibliography of his most important publications.

Edgar Allen, *President*
Henry H. Turner, *Secretary*

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The Journal of CLINICAL ENDOCRINOLOGY

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December, 1941
Volume 1, Number 12

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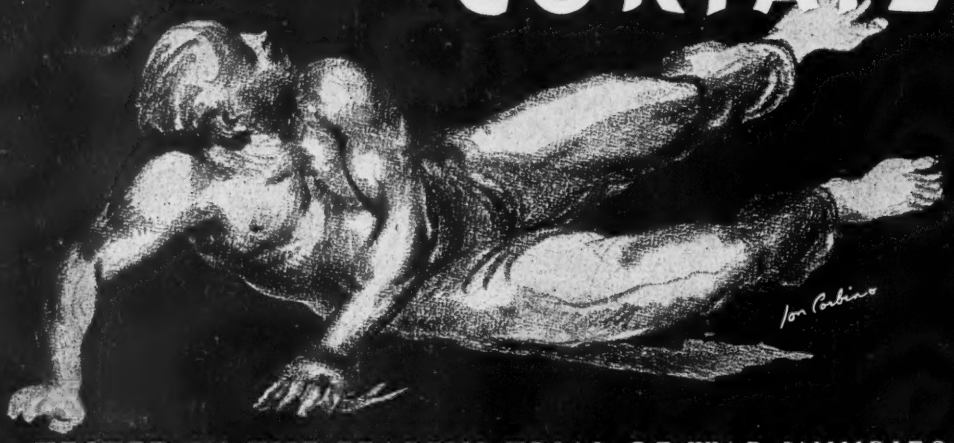

TESTED IN THE FEARFUL TRIAL OF WAR INJURIES

Desoxycorticosterone acetate has been shown to be a life-saving measure against shock due to trauma and burns. Tested in the critical calm of peacetime clinical experience... CORTATE has been shown to be of great value in preventing burn shock, in speeding recovery from surgical operations, great and small, and in minimizing complications... CORTATE is Schering's desoxycorticosterone acetate, hormone of the adrenal cortex having highest power to control blood electrolyte disturbances ensuing upon trauma. By means of the CORTATE ROUTINE, debilitated surgical patients were brought through difficult major operations in strikingly good condition, often giving "the impression that they had not experienced a major operation". By means of urgent dosage with desoxycorticosterone acetate, many victims of the Flanders disaster survived notwithstanding burns over more than half the body surface, complicated by exhaustion, starvation and immersion in the sea. CORTATE* is indicated in these and in other clinical applications where powerful control of the effects of anesthesia, tissue destruction, dehydration and intoxication may be life-saving. Additional data available upon request. *Trade-Mark Reg. U.S. Pat. Off.

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